



METALLOPROTEINASES AND METHODS OF USE THEREFOR

TECHNICAL FIELD

5 The present invention relates generally to compositions and methods for the treatment of conditions associated with undesirable levels of metalloproteinase activity. The invention is more particularly related to metalloproteinases and agents that modulate the activity of such metalloproteinases which may be used, for example, for the therapy of diseases characterized by neuroinflammation and/or
10 neurodegeneration, as well as autoimmune diseases, cancer and inflammation.

BACKGROUND OF THE INVENTION

 The ADAMs (A Disintegrin and Metalloproteinase Domain) are a family of proteins that have both a metalloproteinase domain and disintegrin domain. The
15 ADAMs are membrane anchored proteins that contain homology to snake venom metalloproteases (SVMPs) and disintegrins. This family of proteins now contains over 20 members that have a wide variety of important proteolytic and cell fusion functions. ADAM 17/TACE and ADAM 10/Kuz function as proteases that cleave membrane bound tumor necrosis factor (TNF) and the extracellular domain of Notch, respectively.
20 Other ADAM family members, such as ADAM 1/fertilin α , are proteolytically processed to remove the metalloprotease domain but retain the disintegrin domain. This protein has been shown to be essential for sperm-egg cell fusion.

 A closely related family called ADAMTS contains a thrombospondin domain in addition to the disintegrin and metalloproteinase domains. ADAMTS-1, for
25 example, is expressed in association with inflammatory processes and in a cachexigenic colon carcinoma cell line (see Kuno et al., *J. Biol. Chem.* 272:556-562, 1997; Kuno et al., *Genomics* 46:466-471, 1997). This protein appears to be secreted from the cell and subsequently associated with the extracellular matrix (ECM).

 While the function of ADAMTS-1 and many of the ADAM proteins is
30 not known, it has been shown that ADAM 17 (TACE) processes TNF from the surface of the cell (see Black et al., *Nature* 385:729-733, 1997). ADAM 10 (Kuzbanian) has

also been shown to cleave TNF from the cell surface (Rosendahl et al., *J. Biol. Chem.* 272:24588-24593, 1997). ADAM 10 may be involved in the cleavage of other cell surface proteins as well. In *Drosophila*, ADAM 10 has been reported to cleave the cell surface proteins Notch (Pan and Rubin, *Cell* 90:271-280, 1997) and Delta (Qi et al.,
5 *Science* 283:91-94, 1999). Based largely on these results it is thought that ADAMs proteases are involved in the cleavage of proteins, including growth factors, cytokines and proteoglycans, from the cell surface.

Metalloproteinase activity has been linked to cancer metastasis. The activity of metalloproteinases can contribute to the development of neurodegeneration
10 and inflammation as well. In order to develop agents capable of selectively modulating the activity of a metalloproteinase that contributes to a human disease, it is important to identify and characterize additional metalloproteinases, such as members of the ADAMTS family, and agents that modulate an activity of such metalloproteinases. The present invention fulfills this need and further provides other related advantages.

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SUMMARY OF THE INVENTION

Briefly stated, the present invention provides ADAMTS polypeptides, and methods employing such polypeptides. Within certain aspects, isolated polynucleotides that encode an ADAMTS polypeptide are provided. Certain ADAMTS
20 polynucleotides encode an ADAMTS polypeptide that comprises: (a) at least 50 consecutive amino acid residues of an ADAMTS protein that comprises a sequence recited in any one of SEQ ID NOs:2, 4, 10, 14, 16, 18, 22, 24, 26 or 27; or (b) a variant of any of the foregoing amino acid sequences that differs in one or more substitutions, deletions, additions and/or insertions, wherein substitutions, if any, are present at no
25 more than 10% of the consecutive residues of the ADAMTS protein. Such polynucleotides may, within certain embodiments, comprise a sequence recited in any one of SEQ ID NOs:1, 3, 9, 13, 15, 17, 21, 23 or 25.

Within related aspects, the present invention provides recombinant expression vectors comprising an ADAMTS polynucleotide, as well as host cells
30 transformed or transfected with such an expression vector.

The present invention further provides isolated antisense polynucleotides complementary to at least 20 consecutive nucleotides present within an ADAMTS polynucleotide.

Within further aspects, methods are provided for preparing an ADAMTS polypeptide, comprising the steps of: (a) culturing a host cell transformed or transfected with an expression vector comprising a polynucleotide that encodes an ADAMTS polypeptide comprising: (i) at least 50 consecutive amino acid residues of an ADAMTS protein that comprises a sequence recited in any one of SEQ ID NOs:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26 or 27; or (ii) a variant of any of the foregoing amino acid sequences that differs in one or more substitutions, deletions, additions and/or insertions, wherein substitutions, if any, are present at no more than 10% of the consecutive residues of the ADAMTS protein; wherein the step of culturing is performed under conditions promoting expression of the polynucleotide sequence; and (b) recovering an ADAMTS polypeptide.

The present invention further provides isolated ADAMTS polypeptides comprising: (a) at least 50 consecutive amino acid residues of an ADAMTS protein that comprises a sequence recited in any one of SEQ ID NOs:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26 or 27; or (b) a variant of any of the foregoing amino acid sequences that differs in one or more substitutions, deletions, additions and/or insertions, wherein substitutions, if any, are present at no more than 10% of the consecutive residues of the ADAMTS protein. Such an ADAMTS polypeptide may have an ADAMTS activity that is not substantially diminished relative to the ADAMTS protein. ADAMTS polypeptide may comprise an amino acid sequence recited in any one of SEQ ID NOs:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26 or 27.

Within further aspects, the present invention provides pharmaceutical compositions comprising: (a) an ADAMTS polypeptide comprising: (i) at least 50 consecutive amino acid residues of an ADAMTS protein that comprises a sequence recited in any one of SEQ ID NOs:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26 or 27; or (ii) a variant of any of the foregoing amino acid sequences that differs in one or more substitutions, deletions, additions and/or insertions, wherein substitutions, if any, are

present at no more than 10% of the consecutive residues of the ADAMTS protein; and
(b) a physiologically acceptable carrier.

Vaccines are also provided, comprising: (a) an ADAMTS polypeptide comprising: (i) at least 50 consecutive amino acid residues of an ADAMTS protein that
5 comprises a sequence recited in any one of SEQ ID NOs:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26 or 27; or (ii) a variant of any of the foregoing amino acid sequences that differs in one or more substitutions, deletions, additions and/or insertions, wherein substitutions, if any, are present at no more than 10% of the consecutive residues of the ADAMTS protein; and (b) a non-specific immune response enhancer.

10 Within further aspects, the present invention provides isolated antibodies, or antigen-binding fragments thereof, that specifically bind to an ADAMTS polypeptide comprising a sequence recited in any one of SEQ ID NOs:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26 or 27.

The present invention further provides methods for screening for agents
15 that modulate ADAMTS protein expression or activity. Within certain such aspects, methods are provided for screening for an agent that modulates ADAMTS protein expression in a cell, comprising: (a) contacting a candidate modulator with a cell expressing an ADAMTS polypeptide, wherein the polypeptide comprises: (i) at least 50 consecutive amino acid residues of an ADAMTS protein that comprises a sequence
20 recited in any one of SEQ ID NOs:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26 or 27; or (ii) a variant of any of the foregoing amino acid sequences that differs in one or more substitutions, deletions, additions and/or insertions, wherein substitutions, if any, are present at no more than 10% of the consecutive residues of the ADAMTS protein; and (b) subsequently evaluating the effect of the candidate modulator on expression of an
25 ADAMTS mRNA or polypeptide, and therefrom identifying an agent that modulates ADAMTS protein expression in the cell. Similar screens may be performed using a cell comprising an ADAMTS gene promoter operably linked to a reporter gene, and evaluating the effect of a candidate modulator on expression of the reporter gene.

Within further such aspects, methods are provided for screening for an
30 agent that modulates an ADAMTS protein activity, comprising: (a) contacting a

candidate modulator with an ADAMTS polypeptide, comprising: (i) at least 50 consecutive amino acid residues of an ADAMTS protein that comprises a sequence recited in any one of SEQ ID NOs:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26 or 27; or (ii) a variant of any of the foregoing amino acid sequences that differs in one or more substitutions, deletions, additions and/or insertions, wherein substitutions, if any, are present at no more than 10% of the consecutive residues of the ADAMTS protein; wherein the polypeptide has an ADAMTS activity that is not substantially diminished relative to the ADAMTS protein; and wherein the step of contacting is carried out under conditions and for a time sufficient to allow the candidate modulator to interact with the polypeptide; and (b) subsequently evaluating the effect of the candidate modulator on an ADAMTS activity of the polypeptide, and therefrom identifying an agent that modulates an activity of an ADAMTS protein.

ADAMTS polynucleotides, polypeptides and modulating agents may be used for a variety of therapeutic applications. Within certain aspects, methods are provided herein for inhibiting neuroinflammation and/or neurodegeneration in a patient, comprising administering to a patient an agent that decreases an activity of an ADAMTS protein that comprises a sequence recited in any one of SEQ ID NOs:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26 or 27. Certain such agents may inhibit expression of an endogenous ADAMTS gene or may bind to an ADAMTS protein.

Within related aspects, methods are provided for treating a patient afflicted with a condition associated with neuroinflammation and/or neurodegeneration, comprising administering to a patient a pharmaceutical composition as described above, and thereby alleviating one or more symptoms of a condition associated with neuroinflammation and/or neurodegeneration. Such conditions include Alzheimer's disease, Parkinson's disease and stroke.

Methods are further provided for treating a patient afflicted with a condition associated with cell proliferation, cell migration, inflammation and/or angiogenesis, comprising administering to a patient a pharmaceutical composition as described above and thereby alleviating one or more symptoms of a condition associated with neuroinflammation and/or neurodegeneration.

Within further aspects, methods are provided for treating a patient afflicted with an invasive tumor, a brain tumor or a brain injury, comprising administering to a patient an agent that decreases expression or activity of an ADAMTS protein that comprises a sequence recited in any one of SEQ ID NOs:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26 or 27.

Methods are further provided for modulating ADAMTS expression and/or activity in a cell, comprising contacting a cell expressing an ADAMTS polypeptide with an effective amount of an agent that modulates ADAMTS activity, wherein the ADAMTS polypeptide comprises: (i) at least 50 consecutive amino acid residues of an ADAMTS protein that comprises a sequence recited in any one of SEQ ID NOs:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26 or 27; or (ii) a variant of any of the foregoing amino acid sequences that differs in one or more substitutions, deletions, additions and/or insertions, wherein substitutions, if any, are present at no more than 10% of the consecutive residues of the ADAMTS protein; and thereby modulating ADAMTS expression and/or activity in the cell.

These and other aspects of the present invention will become apparent upon reference to the following detailed description and attached drawings. All references disclosed herein are hereby incorporated by reference in their entirety as if each was incorporated individually.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 presents the sequence of a polynucleotide encoding the representative human metalloproteinase ADAMTS-2 (SEQ ID NO:1).

Figure 2 presents the predicted amino acid sequence of the representative human metalloproteinase ADAMTS-2 (SEQ ID NO:2).

Figures 3A-3B present a partial sequence of a polynucleotide encoding the representative rat metalloproteinase ADAMTS-4 (SEQ ID NO:3).

Figure 4 presents a partial predicted amino acid sequence of the representative rat metalloproteinase ADAMTS-4 (SEQ ID NO:4).

Figures 5A and 5B present the sequence of a polynucleotide encoding the representative human metalloproteinase KIAA0605 (SEQ ID NO:5).

Figure 6 presents the predicted amino acid sequence of the representative human metalloproteinase KIAA0605 (SEQ ID NO:6).

5 Figures 7A and 7B present the sequence of a polynucleotide encoding the representative human metalloproteinase KIAA0366 (SEQ ID NO:7).

Figure 8 presents the predicted amino acid sequence of the representative human metalloproteinase KIAA0366 (SEQ ID NO:8).

Figures 9A and 9B present the sequence of a polynucleotide encoding
10 the representative human metalloproteinase ADAMTS-3 (SEQ ID NO:9).

Figure 10 presents the predicted amino acid sequence of the representative human metalloproteinase ADAMTS-3 (SEQ ID NO:10).

Figures 11A and 11B present the sequence of a polynucleotide encoding the representative human metalloproteinase KIAA0688 (SEQ ID NO:11).

15 Figure 12 presents the predicted amino acid sequence of the representative human metalloproteinase KIAA0688 (SEQ ID NO:12).

Figure 13 presents the sequence of a polynucleotide encoding the representative rat metalloproteinase ADAMTS-5 (SEQ ID NO:13).

Figure 14 presents the predicted amino acid sequence of the
20 representative rat metalloproteinase ADAMTS-5 (SEQ ID NO:14).

Figure 15 presents the sequence of a polynucleotide encoding the representative human metalloproteinase ADAMTS-4 (SEQ ID NO:15).

Figure 16 presents the predicted amino acid sequence of the representative human metalloproteinase ADAMTS-4 (SEQ ID NO:16).

25 Figures 17A-17G present a sequence alignment of human ADAMTS-1 (SEQ ID NO:28), ADAMTS-2 (SEQ ID NO:2), ADAMTS-3 (SEQ ID NO:10), ADAMTS-4 (SEQ ID NO:4), KIAA0688 (SEQ ID NO:12), KIAA0366 (SEQ ID NO:8) and KIAA0605 (SEQ ID NO:6).

Figure 18 presents the sequence of a polynucleotide encoding the
30 representative bovine metalloproteinase ADAMTS-4 (SEQ ID NO:17).

Figure 19 presents the predicted amino acid sequence of the representative bovine metalloproteinase ADAMTS-4 (SEQ ID NO:18).

Figure 20 presents the sequence of a polynucleotide encoding the representative bovine metalloproteinase KIAA0688 (SEQ ID NO:19).

5 Figure 21 presents the predicted amino acid sequence of the representative bovine metalloproteinase KIAA0688 (SEQ ID NO:20).

Figure 22 presents the sequence of a polynucleotide encoding the representative human metalloproteinase ADAMTS-5 (SEQ ID NO:21).

10 Figure 23 presents the predicted amino acid sequence of the representative human metalloproteinase ADAMTS-5 (SEQ ID NO:22).

Figure 24 presents the sequence of a polynucleotide encoding the representative rat metalloproteinase ADAMTS-2 (SEQ ID NO:23).

Figure 25 presents the predicted amino acid sequence of the representative rat metalloproteinase ADAMTS-2 (SEQ ID NO:24).

15 Figure 26 presents the sequence of a polynucleotide encoding the representative rat metalloproteinase ADAMTS-3 (SEQ ID NO:25).

Figure 27 presents the predicted amino acid sequence of the representative rat metalloproteinase ADAMTS-3 (SEQ ID NO:26).

20 Figure 28 is a photograph depicting a coumassie blue-stained gel following electrophoresis of 500 micrograms brevican, previously incubated with and without ADAMTS-4 (TS-4) as indicated.

Figure 29 depicts the amino acid sequence of ADAMTS-9 (SEQ ID NO:27). The predicted signal sequence is underlined. The Zn binding, met turn, TSP 1 motif and TSP-1 like submotifs are shaded. Two potential furin cleavage sites are in parenthesis with the most likely cleavage site shaded. A potential "cysteine switch" amino acid is indicated with a star. The start of each domain is indicated with an arrow.

25 Figures 30A-30C illustrate the comparison of ADAMTS-9 to other ADAMTS family members. In Figure 30A, the domain structure of human ADAMTS 9 is compared to human ADAMTS 1-8, and also with the *C. elegans* GON-1 protein.

30 The pro-domain, metalloprotease domain, disintegrin-like domain, initial TSP type 1

repeat, spacer region, and TSP1 like submotifs are outlined. Figure 30B shows the consensus sequence for Zn binding in the metalloprotease domain (SEQ ID NO:30), along with the Zn binding site for various ADAM and ADAM-TS proteins (SEQ ID Nos: 42-48, 50) that have active metalloprotease domains for comparison to ADAMTS-9 (SEQ ID NO:49). Conserved residues are shaded. Figure 30C is a dendrogram showing the phylogenetic relationship between the protein sequence of the known ADAM-TS human family members and GON-1 from *C. elegans*.

Figure 31 is a photograph illustrating the tissue distribution pattern of ADAMTS-9 in human fetal and adult cDNA. PCR analysis of several human fetal and adult cDNAs was performed using specific primers to ADAMTS 9. Lanes 2 -16 are human adult tissue cDNAs and lanes 17 - 24 are human fetal cDNAs. Lane 25 is a no cDNA control. The expected product size for these ADAMTS 9 primers is 510 bp. The lower panel contains the same cDNA samples used as a template for PCR with G3PDH primers (expected product size is 1 kb).

Figures 32A and 32B illustrate the chromosomal localization of human ADAMTS-9 to 3p14.3-21.1. Figure 32A is a photograph showing the results of FISH analysis in which a genomic ADAMTS 9 probe hybridized to chromosome 3p. Figure 32B shows two ideograms illustrating the chromosomal position of ADAMTS-9 at 3p14.2-14.3. The International System for Human Cytogenetic Nomenclature 1995 was used.

DETAILED DESCRIPTION OF THE INVENTION

As noted above, the present invention is generally directed to polypeptides comprising a member of the ADAMTS family of metalloproteinases, or a variant thereof. Such ADAMTS polypeptides are generally characterized by homology to a known ADAMTS protein, and by the presence of one or more of: (a) a disintegrin domain, (b) a zinc-dependent metalloproteinase domain, (c) an ECM domain and/or (d) a thrombospondin type I motif, which may be identified as described herein. The present invention further provides ADAMTS polynucleotides encoding such polypeptides and agents that modulate an activity of such polypeptides. ADAMTS

polypeptides, polynucleotides and/or modulating agents may generally be used for treating conditions associated with undesirable levels of metalloproteinase activity.

ADAMTS POLYNUCLEOTIDES

5 Any polynucleotide that encodes an ADAMTS polypeptide as described herein is encompassed by the present invention. Such polynucleotides may be single-stranded (coding or antisense) or double-stranded, and may be DNA (genomic, cDNA or synthetic) or RNA molecules. Additional coding or non-coding sequences may, but need not, be present within a polynucleotide of the present invention, and a
10 polynucleotide may, but need not, be linked to other molecules and/or support materials.

ADAMTS polynucleotides may comprise a native ADAMTS sequence (*i.e.*, an ADAMTS gene that can be found in an organism that is not genetically modified), or may comprise a variant of such a sequence. Native ADAMTS sequences
15 encompassed by the present invention include DNA and RNA molecules that comprise a sequence recited in any one of SEQ ID NOs:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23 or 25 as well as homologues thereof from other species and other native ADAMTS sequences that may be identified based on homology to a sequence recited herein. Polynucleotide variants may contain one or more substitutions, additions, deletions
20 and/or insertions such that an ADAMTS activity of the encoded polypeptide is not diminished, relative to a native ADAMTS protein. The effect on an activity of the encoded polypeptide may generally be assessed as described herein. Preferred variants contain nucleotide substitutions, deletions, insertions and/or additions at no more than 30%, preferably at no more than 20% and more preferably at no more than 10%, of the
25 nucleotide positions. Certain variants are substantially homologous to a native gene, or a portion or complement thereof. Such polynucleotide variants are capable of hybridizing under moderately stringent conditions to a naturally occurring DNA sequence encoding an ADAMTS polypeptide (or a complementary sequence). Suitable moderately stringent conditions include prewashing in a solution of 5 X SSC, 0.5%
30 SDS, 1.0 mM EDTA (pH 8.0); hybridizing at 50°C-65°C, 5 X SSC, overnight; followed

by washing twice at 65°C for 20 minutes with each of 2X, 0.5X and 0.2X SSC containing 0.1% SDS). Such hybridizing DNA sequences are also within the scope of this invention.

It will be appreciated by those of ordinary skill in the art that, as a result of the degeneracy of the genetic code, there are many nucleotide sequences that encode a polypeptide as described herein. Some of these polynucleotides bear minimal homology to the nucleotide sequence of any native gene. Nonetheless, polynucleotides that vary due to differences in codon usage are specifically contemplated by the present invention.

A portion of a sequence complementary to a coding sequence (*i.e.*, an antisense polynucleotide) may also be used as a probe or to modulate gene expression. Alternatively, an antisense molecule may be designed to hybridize with a control region of a gene (*e.g.*, promoter, enhancer or transcription initiation site), and block transcription of the gene; or to block translation by inhibiting binding of a transcript to ribosomes. Antisense oligonucleotides may be synthesized directly, or cDNA constructs that can be transcribed into antisense RNA may be introduced into cells or tissues to facilitate the production of antisense RNA. Antisense oligonucleotides are preferably at least 20 nucleotides in length, preferably at least 30 nucleotides in length. A portion of a coding sequence or a complementary sequence may also be designed as a probe or primer to detect gene expression. Probes may be labeled by a variety of reporter groups, such as radionuclides and enzymes, and are preferably at least 10 nucleotides in length, more preferably at least 20 nucleotides in length and still more preferably at least 30 nucleotides in length. Primers are preferably 22-30 nucleotides in length.

ADAMTS polynucleotides may be prepared using any of a variety of techniques. For example, an ADAMTS polynucleotide may be amplified from cDNA prepared from cells that express an ADAMTS protein (*e.g.*, microglia, macrophages, myeloid cells, lymphocytes, astrocytes oligodendrocytes, glial cells, neurons, epithelial cells and/or endothelial cells). Such polynucleotides may be amplified via polymerase chain reaction (PCR). For this approach, sequence-specific primers may be designed

based on the sequences provided herein, and may be purchased or synthesized. An amplified portion may then be used to isolate a full length gene from a human genomic DNA library or from a suitable cDNA library, using well known techniques. Alternatively, a full length gene can be constructed from multiple PCR fragments. ADAMTS polynucleotides may also be prepared by synthesizing oligonucleotide components (which may be derived from sequences provided herein), and ligating components together to generate the complete polynucleotide. One other approach is to screen a library with a synthesized oligonucleotide that hybridizes to an ADAMTS gene. Libraries may generally be prepared and screened using methods well known to those of ordinary skill in the art, such as those described in Sambrook et al., *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Laboratories, Cold Spring Harbor, NY, 1989. It has been found, within the context of the present invention, that ADAMTS genes are expressed in glia. Accordingly, one suitable library is a microglia (e.g., rat) cDNA library. Other libraries that may be employed will be apparent to those of ordinary skill in the art.

As noted above, polynucleotides comprising portions and other variants of native ADAMTS sequences are within the scope of the present invention. Such polynucleotides may generally be prepared by any method known in the art, including chemical synthesis by, for example, solid phase phosphoramidite chemical synthesis. Alternatively, RNA molecules may be generated by *in vitro* or *in vivo* transcription of DNA sequences encoding an ADAMTS polypeptide, provided that the DNA is incorporated into a vector with a suitable RNA polymerase promoter (such as T7 or SP6). Variants may also be generated by mutagenesis or enzymatic digestion of native sequences. Certain polynucleotides may be used to prepare an encoded polypeptide, as described herein. In addition, or alternatively, a polynucleotide may be administered to a patient such that the encoded polypeptide is generated *in vivo*.

Any polynucleotide may be further modified to increase stability *in vivo*. Possible modifications include, but are not limited to, the addition of flanking sequences at the 5' and/or 3' ends; the use of phosphorothioate or 2' O-methyl rather than phosphodiesterase linkages in the backbone; and/or the inclusion of nontraditional

bases such as inosine, queosine and wybutosine, as well as acetyl- methyl-, thio- and other modified forms of adenine, cytidine, guanine, thymine and uridine.

Nucleotide sequences as described herein may be joined to a variety of other nucleotide sequences using established recombinant DNA techniques. For example, a polynucleotide may be cloned into any of a variety of cloning vectors, including plasmids, phagemids, lambda phage derivatives and cosmids. Vectors of particular interest include expression vectors, replication vectors, probe generation vectors and sequencing vectors. In general, a vector will contain an origin of replication functional in at least one organism, convenient restriction endonuclease sites and one or more selectable markers. Other elements will depend upon the desired use, and will be apparent to those of ordinary skill in the art.

Within certain embodiments, polynucleotides may be formulated so as to permit entry into a cell of a mammal, and expression therein. Those of ordinary skill in the art will appreciate that there are many ways to achieve expression of a polynucleotide in a target cell, and any suitable method may be employed. For example, a polynucleotide may be incorporated into a viral vector such as, but not limited to, adenovirus, adeno-associated virus, retrovirus, or vaccinia or other pox virus (e.g., avian pox virus). Techniques for incorporating DNA into such vectors are well known to those of ordinary skill in the art. A retroviral vector may additionally transfer or incorporate a gene for a selectable marker (to aid in the identification or selection of transduced cells) and/or a targeting moiety, such as a gene that encodes a ligand for a receptor on a specific target cell, to render the vector target specific. Targeting may also be accomplished using an antibody, by methods known to those of ordinary skill in the art.

Other formulations for polynucleotides for therapeutic purposes include colloidal dispersion systems, such as macromolecule complexes, nanocapsules, microspheres, beads, and lipid-based systems including oil-in-water emulsions, micelles, mixed micelles, and liposomes. A preferred colloidal system for use as a delivery vehicle *in vitro* and *in vivo* is a liposome (*i.e.*, an artificial membrane vesicle). The preparation and use of such systems is well known in the art.

ADAMTS POLYPEPTIDES

As used herein, the term "ADAMTS polypeptide" encompasses amino acid chains of any length. For example, an ADAMTS polypeptide may comprise a full length endogenous (*i.e.*, native) ADAMTS protein. Such an ADAMTS polypeptide may consist entirely of a native ADAMTS sequence, or may contain additional heterologous sequences. Native ADAMTS proteins may generally be identified based on sequence homology to known ADAMTS protein sequences, such as the representative sequences provided herein, particularly within disintegrin, metalloproteinase and/or thrombospondin motifs. In general, a protein is considered to be an ADAMTS protein if at least 20 consecutive amino acid residues, preferably 40 consecutive amino acids, are identical to a known ADAMTS protein. Alternatively, or in addition, an ADAMTS protein may comprise at least 100 consecutive amino acids that are substantially similar to residues within a known ADAMTS metalloproteinase. "Substantial similarity," as used herein, refers to a sequence that is at least 50% identical, and preferably at least 80% identical.

An ADAMTS protein further comprises one or more of: (a) a disintegrin domain, (b) a zinc-dependent metalloproteinase domain and/or (c) a thrombospondin type I motif; and displays at least one, activity characteristic of such a domain or motif. In general a disintegrin domain serves as an integrin binding loop and has a sequence similar to AVN(E/D)CD (SEQ ID NO:29). Disintegrin domains can also contain the sequence RGD. The metalloproteinase domain is based on the presence of an extended catalytic site consensus sequence (HEXXHXXGXXHD; SEQ ID NO:30). It is thought that the three histidines bind the zinc, the glutamic acid is the catalytic base and the glycine allows an important structural turn (Stocker et al., *Protein Science* 4:823-840, 1995). The thrombospondin domain contains the sequence motif CSRTCG (SEQ ID NO:31).

Another domain that may be present within an ADAMTS protein is a domain that binds to the extracellular matrix. This has been referred to as the ECM domain and has the semiconserved sequence FREEQC (SEQ ID NO:32).

In certain embodiments, amino acid residues within a "substantially similar" region may contain primarily or entirely conservative substitutions. A conservative substitution is one in which an amino acid is substituted for another amino acid that has similar properties, such that one skilled in the art of peptide chemistry would expect the secondary structure and hydrophobic nature of the polypeptide to be substantially unchanged. Amino acid substitutions may generally be made on the basis of similarity on polarity, charge, solubility, hydrophobicity, hydrophilicity and/or the amphipathic nature of the residues. For example, negatively charged amino acids include aspartic acid and glutamic acid; positively charged amino acids include lysine and arginine; and amino acids with uncharged polar head groups having similar hydrophilicity values include leucine, isoleucine and valine; glycine and alanine; asparagine and glutamine; and serine, threonine, phenylalanine and tyrosine. Other groups of amino acids that may represent conservative changes include: (1) ala, pro, gly, glu, asp, gln, asn, ser, thr; (2) cys, ser, tyr, thr; (3) val, ile, leu, met, ala, phe; (4) lys, arg, his; and (5) phe, tyr, trp, his.

An ADAMTS polypeptide may comprise a portion of a native ADAMTS protein. Such a portion is preferably at least 20 consecutive amino acid residues in length, more preferably at least 50 consecutive amino acid residues in length. Within certain embodiments, the portion retains an ADAMTS activity that is not substantially diminished relative to the full length ADAMTS protein. Certain ADAMTS polypeptides comprise a sequence recited in any one of SEQ ID NOs:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26 or 27.

Alternatively, an ADAMTS polypeptide may comprise a variant of an ADAMTS protein or portion thereof. A "variant" is a polypeptide that differs in sequence from a native ADAMTS protein only in substitutions, deletions, insertions and/or additions. Within certain embodiments, substitutions are made (if at all) at no more than 30%, preferably at no more than 20% and more preferably at no more than 10% of residues within a portion of a native ADAMTS protein, as described above. Substitutions are preferably conservative, as described above. Substitutions, deletions and/or amino acid additions may be made at any location(s) in the polypeptide,

provided that the modification does not diminish at least one ADAMTS activity. Thus, a variant may comprise only a portion of a native ADAMTS sequence. In addition, or alternatively, variants may contain additional amino acid sequences (such as, for example, linkers, tags and/or ligands), preferably at the amino and/or carboxy termini.

5 Such sequences may be used, for example, to facilitate purification, detection or cellular uptake of the polypeptide.

Certain variants retain an activity of the native ADAMTS protein. In other words, the variant has a metalloproteinase activity; (2) functions as an integrin ligand (*i.e.*, binds to an integrin), as determined by any standard binding assay; and/or
10 (3) retains a functional thrombospondin motif. Such a variant may have an ADAMTS activity that is not substantially diminished relative to the ADAMTS protein. In other words, the ADAMTS activity of the variant may be enhanced or unchanged, relative to the native protein, or may be diminished by less than 50%, and preferably less than 20%, relative to the native protein.

15 Also encompassed by the present invention are splice variants of an ADAMTS protein. Such variants may have one or more of the domains described herein deleted, or one or more such domains may be replaced by a domain providing a different function. Such splice variants may be identified using amplification or hybridization techniques described herein.

20 Dominant negative forms of ADAMTS proteins are also provided. Such forms include fragments and variants of an ADAMTS protein that, when introduced to a cell expressing a native ADAMTS protein, inhibit an activity of the native protein. Inhibition of ADAMTS protein activity may be assessed as described herein.

In general, ADAMTS polypeptides may be prepared using any of a
25 variety of techniques that are well known in the art. For example, polypeptides of the present invention may be prepared by expression of recombinant DNA encoding the polypeptide in cultured host cells. Preferably, the host cells are bacteria, yeast, insect or mammalian cells. The recombinant DNA may be cloned into any expression vector suitable for use within the host cell and transfected into the host cell using techniques
30 well known to those of ordinary skill in the art. An expression vector generally contains

a promoter sequence that is active in the host cell. A tissue specific promoter may also be used, as long as it is activated in the target cell. Preferred promoters express the polypeptide at high levels.

Optionally, the construct may contain an enhancer, a transcription
5 terminator, a poly(A) signal sequence, a bacterial or mammalian origin of replication and/or a selectable marker, all of which are well known in the art. Enhancer sequences may be included as part of the promoter region used or separately. Transcription terminators are sequences that stop RNA polymerase-mediated transcription. The poly(A) signal may be contained within the termination sequence or incorporated
10 separately. A selectable marker includes any gene that confers a phenotype on the host cell that allows transformed cells to be identified. Such markers may confer a growth advantage under specified conditions. Suitable selectable markers for bacteria are well known and include resistance genes for ampicillin, kanamycin and tetracycline. Suitable selectable markers for mammalian cells include hygromycin, neomycin, genes
15 that complement a deficiency in the host (*e.g.* thymidine kinase and TK⁻ cells) and others well known in the art.

ADAMTS polypeptides may be expressed in transfected cells by culturing the cell under conditions promoting expression of the transfected polynucleotide. Appropriate conditions will depend on the specific host cell and
20 expression vector employed, and will be readily apparent to those of ordinary skill in the art. For commercially available expression vectors, the polypeptide may generally be expressed according to the manufacturer's instructions. Expressed polypeptides of this invention are generally isolated in substantially pure form. Preferably, the polypeptides are isolated to a purity of at least 80% by weight, more preferably to a
25 purity of at least 95% by weight, and most preferably to a purity of at least 99% by weight. In general, such purification may be achieved using, for example, the standard techniques of ammonium sulfate fractionation, SDS-PAGE electrophoresis, and/or affinity chromatography.

Such techniques may be used to prepare native polypeptides or variants
30 thereof. For example, variants of a native polypeptide may generally be prepared from

polynucleotide sequences modified via standard mutagenesis techniques, such as oligonucleotide-directed site-specific mutagenesis, and sections of the DNA sequence may be removed to permit preparation of truncated polypeptides. Portions and other variants having fewer than about 100 amino acids, and generally fewer than about 50
5 amino acids, may also be generated by synthetic means, using techniques well known to those of ordinary skill in the art. For example, such polypeptides may be synthesized using any of the commercially available solid-phase techniques, such as the Merrifield solid-phase synthesis method, where amino acids are sequentially added to a growing amino acid chain. See Merrifield, *J. Am. Chem. Soc.* 85:2149-2146, 1963. Equipment
10 for automated synthesis of polypeptides is commercially available from suppliers such as Applied BioSystems, Inc. (Foster City, CA), and may be operated according to the manufacturer's instructions.

In general, polypeptides and polynucleotides as described herein are isolated. An "isolated" polypeptide or polynucleotide is one that is removed from its
15 original environment. For example, a naturally-occurring protein is isolated if it is separated from some or all of the coexisting materials in the natural system. A polynucleotide is considered to be isolated if, for example, it is cloned into a vector that is not a part of the natural environment.

20 EVALUATION OF ADAMTS ACTIVITY

As noted above, native ADAMTS proteins and certain variants thereof possess ADAMTS activity. In other words, such polypeptides (1) possess metalloproteinase activity; (2) are capable of interacting with integrin and/or (3) retain a functional thrombospondin motif. Metalloproteinase activity may generally be
25 evaluated by combining an ADAMTS polypeptide with a suitable substrate, and detecting proteinase activity using any standard technique (e.g., Western blot analysis). In general, a variant of an ADAMTS protein that contains a metalloproteinase domain is said to retain metalloproteinase activity if it displays metalloproteinase activity that is not substantially diminished relative to the metalloproteinase activity of the native

ADAMTS protein. In other words, such activity may be enhanced, unchanged or diminished by less than 10%, relative to the activity of the native ADAMTS protein.

The ability of an ADAMTS protein variant to interact with integrin may be assessed using standard binding assays to detect interaction with a purified recombinant integrin or a cell expressing one or more integrins, either naturally or as a result of transfection with genes encoding an integrin (*see Almeida et al., Cell 81:1095-1104, 1995; Chen et al., J. Cell Biol. 144:549-561, 1999*). Antibodies against various integrins can also be used to interfere with disintegrin-integrin binding and used to further demonstrate specificity of the interaction. In general, a variant of an ADAMTS protein is said to retain the ability to interact with an integrin if such interaction is not substantially diminished relative to the interaction between a native ADAMTS protein and the integrin. In other words, the level of such an interaction may be enhanced, unchanged or diminished by less than 10%, relative to the activity of the native ADAMTS protein.

Thrombospondins have been shown to function in cell adhesion, cell migration, cell proliferation and angiogenesis. A functional thrombospondin motif may be confirmed based on any assay designed to assess such a function. For examples, an ADAMTS protein may inhibit endothelial cell migration, or may inhibit angiogenesis (*e.g., in a rat cornea model; see Nishimori et al., Oncogene 15:2145-2150, 1997*). Alternatively, a functional thrombospondin motif may be detected using an assay to measure binding to CD36 (*see Dawson et al., J. Cell. Biol. 138:707-717, 1997*). Within any such assay, a variant of an ADAMTS protein is said to have a functional thrombospondin motif if the detected thrombospondin function is not substantially diminished relative to that of the native ADAMTS protein. In other words, the function may be enhanced, unchanged or diminished by less than 10%, relative to that of the native ADAMTS protein.

ADAMTS POLYPEPTIDE MODULATING AGENTS

The present invention further provides agents capable of modulating ADAMTS activity. Such agents may function by modulating ADAMTS transcription

or translation, by stabilizing or destabilizing an ADAMTS protein, or by directly inhibiting or enhancing an activity of an ADAMTS protein. Alternatively, an agent may interact with a substrate for the metalloproteinase or with an integrin involved in and interaction with the disintegrin domain of an ADAMTS protein. Preferably, a
5 modulating agent has a minimum of side effects and is non-toxic. For some applications, agents that can penetrate cells or that are targeted to interstitial spaces are preferred.

Modulating agents include substances that selectively bind to an ADAMTS protein. Such substances include antibodies and antigen-binding fragments
10 thereof (*e.g.*, F(ab)₂, Fab, Fv, V_H or V_K fragments), as well as single chain antibodies, multimeric monospecific antibodies or fragments thereof and bi- or multi-specific antibodies and fragments thereof. Antibodies that bind to an ADAMTS protein may be polyclonal or monoclonal, and are specific for an ADAMTS polypeptide (*i.e.*, bind to such a peptide detectable within any appropriate binding assay, and do not bind to an
15 unrelated protein in a similar assay under the same conditions). Preferred antibodies are those antibodies that function as modulating agents to inhibit or block an ADAMTS activity *in vivo*. Antibodies may also be employed within assays for detecting the level of ADAMTS protein within a sample.

Antibodies may be prepared by any of a variety of techniques known to
20 those of ordinary skill in the art (*see, e.g.*, Harlow and Lane, *Antibodies: A Laboratory Manual*, Cold Spring Harbor Laboratory, 1988). In one such technique, an immunogen comprising the polypeptide is initially injected into a suitable animal (*e.g.*, mice, rats, rabbits, sheep and goats), preferably according to a predetermined schedule incorporating one or more booster immunizations, and the animals are bled periodically.
25 Polyclonal antibodies specific for the polypeptide may then be purified from such antisera by, for example, affinity chromatography using the polypeptide coupled to a suitable solid support.

Monoclonal antibodies may be prepared, for example, using the technique of Kohler and Milstein, *Eur. J. Immunol.* 6:511-519, 1976, and improvements
30 thereto. Briefly, these methods involve the preparation of immortal cell lines capable of

producing antibodies having the desired specificity (*i.e.*, reactivity with the polypeptide of interest). Such cell lines may be produced, for example, from spleen cells obtained from an animal immunized as described above. The spleen cells are then immortalized by, for example, fusion with a myeloma cell fusion partner, preferably one that is syngeneic with the immunized animal. For example, the spleen cells and myeloma cells may be combined with a nonionic detergent for a few minutes and then plated at low density on a selective medium that supports the growth of hybrid cells, but not myeloma cells. A preferred selection technique uses HAT (hypoxanthine, aminopterin, thymidine) selection. After a sufficient time, usually about 1 to 2 weeks, colonies of hybrids are observed. Single colonies are selected and tested for binding activity against the polypeptide. Hybridomas having high reactivity and specificity are preferred.

Monoclonal antibodies may be isolated from the supernatants of growing hybridoma colonies. In addition, various techniques may be employed to enhance the yield, such as injection of the hybridoma cell line into the peritoneal cavity of a suitable vertebrate host, such as a mouse. Monoclonal antibodies may then be harvested from the ascites fluid or the blood. Contaminants may be removed from the antibodies by conventional techniques, such as chromatography, gel filtration, precipitation, and extraction.

Once a cell line, such as a hybridoma, expressing an antibody that specifically binds to an ADAMTS protein has been obtained, other chimeric antibodies and fragments thereof as described herein may be prepared. Using well known techniques, a cDNA molecule encoding the antibody may be identified.

Other modulating agents include peptides, and nonpeptide mimetics thereof, that specifically interact with one or more regions of an ADAMTS polypeptide. Such agents may generally be identified using any well known binding assay, such as a representative assay provided herein. For example, such modulating agents may be isolated using well known techniques to screen substances from a variety of sources, such as plants, fungi or libraries of chemicals, small molecules or random peptides.

Other modulating agents may function by inhibiting or enhancing transcription or translation of an ADAMTS gene. For example, modulating agents may include antisense polynucleotides (DNA or RNA), which inhibit the transcription of a native ADAMTS protein. cDNA constructs that can be transcribed into antisense RNA may also be introduced into cells of tissues to facilitate the production of antisense RNA. Antisense technology can generally be used to control gene expression through triple-helix formation, which compromises the ability of the double helix to open sufficiently for the binding of polymerases, transcription factors or regulatory molecules (see Gee et al., *In Huber and Carr, Molecular and Immunologic Approaches*, Futura Publishing Co. (Mt. Kisco, NY; 1994). Alternatively, an antisense molecule may be designed to hybridize with a control region of a gene (e.g., promoter, enhancer or transcription initiation site), and block transcription of the gene; or to block translation by inhibiting binding of a transcript to ribosomes. Antisense polynucleotides are generally at least 10 nucleotides in length, more preferably at least 20 nucleotides in length and still more preferably at least 30 nucleotides in length.

Other agents may modulate transcription by interacting with an ADAMTS promoter. Such agents may be identified using standard assays, following isolation of an endogenous ADAMTS gene promoter region. One method for identifying a promoter region uses a PCR-based method to clone unknown genomic DNA sequences adjacent to a known cDNA sequence. This approach may generate a 5' flanking region, which may be subcloned and sequenced using standard methods. Primer extension and/or RNase protection analyses may be used to verify the transcriptional start site deduced from the cDNA.

To define the boundary of the promoter region, putative promoter inserts of varying sizes may be subcloned into a heterologous expression system containing a suitable reporter gene without a promoter or enhancer may be employed. Internal deletion constructs may be generated using unique internal restriction sites or by partial digestion of non-unique restriction sites. Constructs may then be transfected into cells that display high levels of ADAMTS protein expression. In general, the construct with

the minimum 5' flanking region showing the highest level of expression of reporter gene is identified as the promoter.

To evaluate the effect of a candidate agent on ADAMTS gene transcription, a promoter or regulatory element thereof may be operatively linked to a reporter gene. Such a construct may be transfected into a suitable host cell, which may be used to screen, for example, a combinatorial small molecule library. Briefly, cells are incubated with the library (*e.g.*, overnight). Cells are then lysed and the supernatant is analyzed for reporter gene activity according to standard protocols. Compounds that result in a decrease in reporter gene activity are inhibitors of ADAMTS gene transcription.

For modulating agents that act directly on an ADAMTS protein, an initial screen to assess the ability of candidate agents to bind to such a protein may be employed, although such binding is not essential for a modulating agent. For identifying agents that bind to an ADAMTS polypeptide, any of a variety of binding assays may be employed, such as standard affinity techniques and yeast two-hybrid screens. In general, the amount of candidate modulator added in such screens ranges from about 1 pM to 1 μ M. An antibody or other modulating agent is said to "specifically bind" to an ADAMTS polypeptide if it reacts at a detectable level with such a polypeptide and does not react detectably with unrelated polypeptides. Such antibody binding properties may be assessed using, for example, an ELISA.

Screens for modulating agents that increase the rate of ADAMTS protein synthesis or stabilize ADAMTS protein may be readily performed using well known techniques that detect the level of ADAMTS protein or mRNA. Suitable assays include RNA protection assays, *in situ* hybridization, ELISAs, Northern blots and Western blots. Such assays may generally be performed using standard methods (*see* Sambrook et al., *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Laboratories, Cold Spring Harbor, NY, 1989). For example, to detect mRNA encoding ADAMTS protein, a nucleic acid probe complementary to all or a portion of an ADAMTS gene sequence may be employed in a Northern blot analysis of mRNA prepared from suitable cells (*e.g.*, brain, lung, heart, spleen, spinal cord, testis, astrocytes or microglia).

To detect ADAMTS protein, a reagent that binds to the protein (typically an antibody) may be employed within an ELISA or Western assay. Following binding, a reporter group suitable for direct or indirect detection of the reagent is employed (*i.e.*, the reporter group may be covalently bound to the reagent or may be bound to a second molecule, such as Protein A, Protein G, immunoglobulin or lectin, which is itself capable of binding to the reagent). Suitable reporter groups include, but are not limited to, enzymes (*e.g.*, horseradish peroxidase), substrates, cofactors, inhibitors, dyes, radionuclides, luminescent groups, fluorescent groups and biotin. Such reporter groups may be used to directly or indirectly detect binding of the reagent to a sample component using standard methods known to those of ordinary skill in the art.

To use such assays for identifying a modulating agent, the level of ADAMTS protein or mRNA is evaluated in cells (*e.g.*, astrocytes or microglia) treated with one or more candidate modulating agents. An increase or decrease in ADAMTS levels may be measured by evaluating ADAMTS mRNA and/or protein in the presence and absence of candidate modulating agent. In general, the amount of candidate modulator added in such screens ranges from about 1 pM to 1 μ M. A candidate that results in a statistically significant change in the level of ADAMTS mRNA and/or protein is a modulating agent.

Modulating agents that decrease ADAMTS levels generally inhibit ADAMTS activity. To further evaluate the effect on ADAMTS activity, an assay may be performed as described above in the presence and absence of modulating agent. Agents that bind to a substrate of an ADAMTS protein domain may also be identified using such assays. Modulating agents may generally be administered by addition to a cell culture or by the methods described below for *in vivo* administration.

ADAMTS POLYPEPTIDE AND MODULATING AGENT MODIFICATION AND FORMULATIONS

An ADAMTS polypeptide or modulating agent as described herein may, but need not, be linked to one or more additional molecules. In particular, as discussed below, it may be beneficial for certain applications to link multiple polypeptides and/or modulating agents (which may, but need not, be identical) to a support material, such as

a polymeric matrix or a bead or other particle, which may be prepared from a variety of materials including glass, plastic or ceramics. For certain applications, biodegradable support materials are preferred.

5 Suitable methods for linking an ADAMTS polypeptide or modulating agent to a support material will depend upon the composition of the support and the intended use, and will be readily apparent to those of ordinary skill in the art. Attachment may generally be achieved through noncovalent association, such as adsorption or affinity or, preferably, via covalent attachment (which may be a direct linkage or may be a linkage by way of a cross-linking agent).

10 It may be beneficial for certain applications to link an ADAMTS polypeptide or modulating agent to a targeting agent to facilitate targeting to one or more specific tissues. As used herein, a "targeting agent," may be any substance (such as a compound or cell) that, when linked to a polypeptide or modulating agent enhances the transport of the polypeptide or modulating agent to a target tissue, thereby
15 increasing the local concentration. Targeting agents include antibodies or fragments thereof, receptors, ligands and other molecules that bind to cells of, or in the vicinity of, the target tissue. Known targeting agents include serum hormones, antibodies against cell surface antigens, lectins, adhesion molecules, tumor cell surface binding ligands, steroids, cholesterol, lymphokines, fibrinolytic enzymes and those drugs and proteins
20 that bind to a desired target site. An antibody targeting agent may be an intact (whole) molecule, a fragment thereof, or a functional equivalent thereof. Linkage is generally covalent and may be achieved by, for example, direct condensation or other reactions, or by way of bi- or multi-functional linkers. Within other embodiments, it may also be possible to target a polynucleotide encoding a polypeptide or modulating agent to a
25 target tissue, thereby increasing the local concentration. Such targeting may be achieved using well known techniques, including retroviral and adenoviral infection. To treat a patient afflicted with certain conditions (e.g., neurodegenerative conditions), it may be beneficial to deliver an ADAMTS polypeptide, polynucleotide or modulating agent to the intracellular space. Such targeting may be achieved using well known

techniques, such as through the use of polyethylene glycol or liposomes, as described in Turrens, *Xenobiotica* 21:1033-1040, 1991.

For certain embodiments, it may be beneficial to also, or alternatively, link a drug to a polypeptide or modulating agent. As used herein, the term "drug" refers to any bioactive agent intended for administration to a mammal to prevent or treat a disease or other undesirable condition.

Within certain aspects of the present invention, one or more polypeptides, polynucleotides or modulating agents as described herein may be present within a pharmaceutical composition or vaccine. A pharmaceutical composition further comprises one or more pharmaceutically or physiologically acceptable carriers, diluents or excipients. Vaccines may comprise one or more such compounds and a non-specific immune response enhancer. A non-specific immune response enhancer may be any substance that enhances an immune response to an exogenous antigen. Examples of non-specific immune response enhancers include adjuvants and liposomes.

To prepare a pharmaceutical composition, an effective amount of one or more polypeptides, polynucleotides and/or modulating agents is mixed with a suitable pharmaceutical carrier. Solutions or suspensions used for parenteral, intradermal, subcutaneous or topical application can include, for example, a sterile diluent (such as water), saline solution, fixed oil, polyethylene glycol, glycerin, propylene glycol or other synthetic solvent; antimicrobial agents (such as benzyl alcohol and methyl parabens); antioxidants (such as ascorbic acid and sodium bisulfite) and chelating agents (such as ethylenediaminetetraacetic acid (EDTA)); buffers (such as acetates, citrates and phosphates). If administered intravenously, suitable carriers include physiological saline or phosphate buffered saline (PBS), and solutions containing thickening and solubilizing agents, such as glucose, polyethylene glycol, polypropylene glycol and mixtures thereof. In addition, other pharmaceutically active ingredients and/or suitable excipients such as salts, buffers and stabilizers may, but need not, be present within the composition.

A pharmaceutical composition is generally formulated and administered to exert a therapeutically useful effect while minimizing undesirable side effects. The

number and degree of acceptable side effects depend upon the condition for which the composition is administered. For example, certain toxic and undesirable side effects that are tolerated when treating life-threatening illnesses, such as tumors, would not be tolerated when treating disorders of lesser consequence. The concentration of active
5 component in the composition will depend on absorption, inactivation and excretion rates thereof, the dosage schedule and the amount administered, as well as other factors that may be readily determined by those of skill in the art.

A polypeptide, polynucleotide or modulating agent may be prepared with carriers that protect it against rapid elimination from the body, such as time release
10 formulations or coatings. Such carriers include controlled release formulations, such as, but not limited to, implants and microencapsulated delivery systems, and biodegradable, biocompatible polymers, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, polyorthoesters, polylactic acid and others known to those of ordinary skill in the art. Such formulations may generally be prepared using well known technology and
15 administered by, for example, oral, rectal or subcutaneous implantation, or by implantation at the desired target site. Sustained-release formulations may contain a polynucleotide, polypeptide or modulating agent dispersed in a carrier matrix and/or contained within a reservoir surrounded by a rate controlling membrane. Preferably the formulation provides a relatively constant level of modulating agent release. The
20 amount of active component contained within a sustained release formulation depends upon the site of implantation, the rate and expected duration of release and the nature of the condition to be treated or prevented.

Pharmaceutical compositions of the present invention may be administered in a manner appropriate to the disease to be treated (or prevented).
25 Administration may be effected by incubation of cells *ex vivo* or *in vivo*, such as by topical treatment, delivery by specific carrier or by vascular supply. Appropriate dosages and a suitable duration and frequency of administration will be determined by such factors as the condition of the patient, the type and severity of the patient's disease and the method of administration. In general, an appropriate dosage and treatment
30 regimen provides the polypeptide, polynucleotide and/or modulating agent(s) in an

amount sufficient to provide therapeutic and/or prophylactic benefit (*i.e.*, an amount that ameliorates the symptoms or treats or delays or prevents progression of the condition). The precise dosage and duration of treatment is a function of the disease being treated and may be determined empirically using known testing protocols or by testing the compositions in model systems known in the art and extrapolating therefrom. Dosages may also vary with the severity of the condition to be alleviated. The composition may be administered one time, or may be divided into a number of smaller doses to be administered at intervals of time. In general, the use of the minimum dosage that is sufficient to provide effective therapy is preferred. Patients may generally be monitored for therapeutic effectiveness using assays suitable for the condition being treated or prevented, which will be familiar to those of ordinary skill in the art, and for any particular subject, specific dosage regimens may be adjusted over time according to the individual need.

For pharmaceutical compositions comprising polynucleotides, the polynucleotide may be present within any of a variety of delivery systems known to those of ordinary skill in the art, including nucleic acid, bacterial and viral expression systems, and colloidal dispersion systems such as liposomes. Appropriate nucleic acid expression systems contain the necessary DNA sequences for expression in the patient (such as a suitable promoter and terminating signal, as described above). The DNA may also be "naked," as described, for example, in Ulmer et al., *Science* 259:1745-1749, 1993.

Various viral vectors that can be used to introduce a nucleic acid sequence into the targeted patient's cells include, but are not limited to, vaccinia or other pox virus, herpes virus, retrovirus, or adenovirus. Techniques for incorporating DNA into such vectors are well known to those of ordinary skill in the art. Preferably, the retroviral vector is a derivative of a murine or avian retrovirus including, but not limited to, Moloney murine leukemia virus (MoMuLV), Harvey murine sarcoma virus (HaMuSV), murine mammary tumor virus (MuMTV), and Rous Sarcoma Virus (RSV). A retroviral vector may additionally transfer or incorporate a gene for a selectable marker (to aid in the identification or selection of transduced cells) and/or a gene that

encodes the ligand for a receptor on a specific target cell (to render the vector target specific).

Viral vectors are typically non-pathogenic (defective), replication competent viruses, which require assistance in order to produce infectious vector particles. This assistance can be provided, for example, by using helper cell lines that contain plasmids that encode all of the structural genes of the retrovirus under the control of regulatory sequences within the LTR, but that are missing a nucleotide sequence which enables the packaging mechanism to recognize an RNA transcript for encapsulation. Such helper cell lines include (but are not limited to) Ψ2, PA317 and PA12. A retroviral vector introduced into such cells can be packaged and vector virion produced. The vector virions produced by this method can then be used to infect a tissue cell line, such as NIH 3T3 cells, to produce large quantities of chimeric retroviral virions.

Another targeted delivery system for polynucleotides is a colloidal dispersion system. Colloidal dispersion systems include macromolecule complexes, nanocapsules, microspheres, beads, and lipid-based systems including oil-in-water emulsions, micelles, mixed micelles, and liposomes. A preferred colloidal system for use as a delivery vehicle *in vitro* and *in vivo* is a liposome (*i.e.*, an artificial membrane vesicle). RNA, DNA and intact virions can be encapsulated within the aqueous interior and delivered to cells in a biologically active form. The preparation and use of liposomes is well known to those of ordinary skill in the art.

THERAPEUTIC APPLICATIONS

As noted above, ADAMTS polynucleotides, polypeptides and modulating agents may generally be used for the therapy of diseases characterized by neuroinflammation or neurodegeneration. In general, ADAMTS metalloproteinases are believed to function in cleaving proteins from cell surfaces (which may be surfaces of cells that synthesize the metalloproteinase or other cells). Pharmaceutical compositions as provided herein may be administered to a patient, alone or in combination with other therapies, to treat or prevent neurodegenerative diseases such as Alzheimer's disease,

Parkinson's disease or stroke. Pharmaceutical compositions provided herein may also be beneficial for therapy of conditions related to cell proliferation, cell migration, inflammation or angiogenesis. Such conditions include cancer, arthritis and autoimmune diseases.

5 Modulation of an ADAMTS function, either *in vitro* or *in vivo*, may generally be achieved by administering a modulating agent that inhibits ADAMTS transcription, translation or activity. In some instances, however, the ADAMTS activity may be lower than is desired. In such cases, polynucleotides, polypeptides and/or modulating agents that enhance ADAMTS activity may be administered. The activity
10 of an endogenous ADAMTS protein within a cell may be increased by, for example, inducing expression of the ADAMTS gene and/or administering a modulating agent that enhances ADAMTS activity. Each of these methods may be performed using mammalian cells in culture or within a mammal, such as a human.

Certain ADAMTS polypeptides may be used to cleave the proteoglycan
15 brevican. Brevican is a brain specific proteoglycan. The secreted form of brevican is upregulated in response to CNS injury and has been implicated in reactive gliosis, and a cleaved form may be important for tumor invasion (*see* Zhang et al., *J. Neuroscience* 18:2370-76, 1998). Thus, brevican cleavage appears to be important in brain injury and gliomas. Modulating agents that inhibit the ability of such ADAMTS polypeptides to
20 cleave brevican may be used to treat brain injuries, brain tumors and other invasive tumors.

Routes and frequency of administration, as well as dosage, will vary from individual to individual, and may be readily established using standard techniques. In general, the pharmaceutical compositions and vaccines may be administered by
25 injection (*e.g.*, intracutaneous, intramuscular, intravenous or subcutaneous), intranasally (*e.g.*, by aspiration) or orally. A suitable dose is an amount of a compound that, when administered as described above, is capable of causing modulation of an ADAMTS activity that leads to an improved clinical outcome (*e.g.*, more frequent remissions, complete or partial or longer disease-free survival) in vaccinated patients as compared
30 to non-vaccinated patients. In general, an appropriate dosage and treatment regimen

provides the active compound(s) in an amount sufficient to provide therapeutic and/or prophylactic benefit. Such a response can be monitored by establishing an improved clinical outcome (*e.g.*, more frequent remissions, complete or partial, or longer disease-free survival) in treated patients as compared to non-treated patients. In general, suitable dose sizes will vary with the size of the patient, but will typically range from about 0.1 mL to about 5 mL.

DIAGNOSTIC APPLICATIONS

In a related aspect of the present invention, kits for detecting ADAMTS proteins are provided. Such kits may be designed for detecting the level of ADAMTS protein or nucleic acid encoding an ADAMTS protein within a sample. In general, the kits of the present invention comprise one or more containers enclosing elements, such as reagents or buffers, to be used in the assay. A kit for detecting the level of ADAMTS protein or nucleic acid typically contains a reagent that binds to the ADAMTS protein, DNA or RNA. To detect nucleic acid, the reagent may be a nucleic acid probe or a PCR primer. To detect protein, the reagent is typically an antibody. A kit may also contain a reporter group suitable for direct or indirect detection of the reagent as described above.

The following Examples are offered by way of illustration and not by way of limitation.

EXAMPLES

Example 15 Preparation of Novel ADAMTS Family Members

This Example illustrates the cloning of cDNA molecules encoding members of the ADAMTS family of metalloproteinases based on induction of expression in rat glial cells by aggregated beta amyloid.

Subtractive hybridization was performed as described (Kelner and Maki,
10 *Methods in Molecular Medicine, vol 22: Neurodegeneration Methods and Protocols*,
Eds J. Harry and H.A. Tilson, Human Press Inc., Totowa, NJ). Briefly, rat glial cells
were cultured and treated with aggregated beta amyloid. After 24 hours, RNA was
prepared from these cells and from control cells that were not treated with beta amyloid.
Genes expressed in the activated cells but not the control cells were sequenced. This
15 screen identified rat ADAMTS-3 (cDNA and encoded protein sequences shown in
Figure 26 (SEQ ID NO:25) and Figure 27 (SEQ ID NO:26), respectively). The rat
cDNA was used to screen a human cDNA library and resulted in the isolation of human
ADAMTS-3. ADAMTS-3 is 2,866 nucleotides in length (Figures 9A and 9B; SEQ ID
NO:9) and codes for a putative protein that is 955 amino acids in length (Figure 10;
20 SEQ ID NO:10). ADAMTS-3 contains a metalloproteinase domain, a disintegrin
domain, thrombospondin motifs and an ECM domain.

Example 225 Preparation of Novel ADAMTS Family Members using Degenerate PCR

This Example illustrates the use of degenerate PCR to clone partial cDNA molecules encoding members of the ADAMTS family of metalloproteinases.

PCR was performed using rat microglia cDNA and degenerate oligonucleotides derived from an analysis of the sequence from ADAMTS-1 and
30 ADAMTS-3. Degenerate primers were designed based on common sequences between

these two genes. The original degenerate primers were designed based on a small region of these two genes that was cloned. One primer had the sequence 5'-TTYMGNGARGARCARTGY-3' (SEQ ID NO:33), while the other primer had the sequence 5'-RCANAYNCCRCAYTTTRTC-3' (SEQ ID NO:34). The PCR conditions
5 were annealing at 47°C for 1 minute, 72°C extension for 2 minutes and 94°C denaturation for 30 seconds.

Following PCR samples were fractionated by gel electrophoresis and fragments of the expected size were cloned into the vector pCRScript and sequenced. One amplified cDNA molecule was designated rat ADAMTS-2 (Figure 24; SEQ ID
10 NO:23), and the encoded protein has the predicted sequence shown in Figure 25 (SEQ ID NO:24). This cDNA was used to screen a human cDNA library, from which human ADAMTS-2 was identified. Human ADAMTS-2 has the sequence shown in Figure 1 (SEQ ID NO:1), and appears to encode the protein recited in Figure 2 (SEQ ID NO:2).

Rat ADAMTS-4 was isolated using the PCR approach and is a
15 polynucleotide having the sequence shown in Figures 3A and 3B (SEQ ID NO:3), which appears to encode the protein recited in Figure 4 (SEQ ID NO:4). For rat ADAMTS-4 the metalloproteinase domain begins at amino acid 260(R), the disintegrin domain begins at residue 487(Q), a thrombospondin motif begins at residue 570(W) and an ECM domain begins at residue 621(C). The rat ADAMTS-4 sequence was used to
20 screen a human cDNA library and human ADAMTS-4 was isolated. Human ADAMTS-4 is 1455 nucleotides in length (Figure 15; SEQ ID NO:15) and codes for a putative protein that is 485 amino acids in length (Figure 16; SEQ ID NO:16). The disintegrin domain in human ADAMTS-4 begins at amino acid 39(E), the start of the first thrombospondin repeat is at amino acid 124(W) and the start of another
25 thrombospondin repeat is at amino acid 479(C). Bovine ADAMTS-4 cDNA has the sequence shown in Figure 18 (SEQ ID NO:17), encoding the predicted amino acid sequence shown in Figure 19 (SEQ ID NO:18).

Rat ADAMTS-5 is a cDNA molecule with the sequence shown in Figure 13 (SEQ ID NO:13), encoding the amino acid sequence shown in Figure 14 (SEQ ID

NO:14). The human ADAMTS cDNA and protein sequences are shown in Figure 22 (SEQ ID NO:21) and Figure 23 (SEQ ID NO:22), respectively.

ADAMTS-4 was further shown to cleave the brain-specific proteoglycan brevican. Five hundred micrograms of purified brevican was cleaved with 500
5 micrograms of human ADAMTS-4 and incubated overnight at 37°C. The cleavage reaction was vacuum dried and resuspended in SDS sample loading dye for running on a 4-20% SDS polyacrylamide gel. Equal amounts of cleaved and uncleaved brevican were added to the gel. After electrophoresis the gel was stained with Coumassie Blue to visualize the protein bands. The results, presented in Figure 30, show that brevican is
10 cleaved upon incubation with ADAMTS-4.

Example 3

Identification of ADAMTS Family Members using Database Searches

15 This Example illustrates the use of database searches to identify cDNA molecules encoding members of the ADAMTS family of metalloproteinases.

To identify additional members of the ADAMTS family, the GenBank database was searched for sequences similar to ADAMTS-1 and ADAMTS-3. This search retrieved KIAA0605 (Figures 5A and 5B; SEQ ID NO:5), which appears to
20 encode a protein of 951 amino acids (Figure 6; SEQ ID NO:6). The coding sequence contains thrombospondin motifs, but no metalloproteinase or disintegrin domains have been identified. A thrombospondin motif begins with amino acid 50(W). Six additional thrombospondin motifs were found beginning with amino acid 568(K). The domain that binds to the extracellular matrix begins with amino acid 105(C).

25 Also retrieved was KIAA0366 (Figures 7A and 7B; SEQ ID NO:7), which appears to encode a protein of 951 amino acids (Figure 8; SEQ ID NO:8), including metalloproteinase and disintegrin domains, as well as thrombospondin motifs. For KIAA0366, the metalloproteinase domain begins with amino acid 241(T), the disintegrin domain begins with amino acid 460(D), a thrombospondin domain is present
30 beginning at position 544(W) and another thrombospondin repeat occurs at position

842(W). The ECM domain begins at amino acid 597(C) and contains the semiconserved sequence FREEQC (SEQ ID NO:32). KIAA0366 does not appear to have a transmembrane domain, and therefore is likely to encode a secreted protein.

An additional sequence identified in this search was KIAA0688 (Figures 11A and 11B; SEQ ID NO:11), which appears to encode the protein shown in Figure 12 and SEQ ID NO:12. This gene codes for a protein with a metalloproteinase domain beginning at amino acid 245(R), a disintegrin domain beginning at amino acid 465(E), a thrombospondin motif at position 550(W), an ECM domain at position 601(C) and two additional thrombospondin motifs at position 905(W). A bovine KIAA0688 cDNA sequence is shown in Figure 20 (SEQ ID NO:19), and the predicted amino acid sequence of the encoded protein is shown in Figure 21 (SEQ ID NO:20).

Figures 17A-17G present an alignment of the ADAMTS protein sequences described herein, along with ADAMTS-1.

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Example 4

Identification and Characterization of ADAMTS-9

This Example illustrates the cloning and characterization of the ADAMTS/metallospodin family member designated herein as ADAMTS-9.

A small fragment of the rat ADAMTS-9 gene was initially cloned from a beta amyloid-treated (35 µg/ml aggregated Aβ 1-42) rat astrocyte cDNA library. DNA sequence analysis was performed using a PCR procedure employing fluorescent dideoxynucleotides and a model ABI-377 automated sequencer (PE Biosystem). BLAST sequence analysis revealed low homology at the protein level to the spacer region of the murine ADAMTS-1 gene.

This clone was labeled with [α -³²P]dCTP using the Prime It II kit (Stratagene) and used to screen a human spinal cord phage library (Clontech) according to the manufacturer's instructions. Positive plaques were purified and lambda DNA prepared (Qiagen). Several overlapping clones were sequenced that had homology to the original rat clone. In order to determine the 5' and 3' ends of the gene RACE (rapid

30

amplification of cDNA ends) analysis was performed using Marathon Ready placenta and fetal cDNA libraries (Clontech) with SMART primers (Clontech). Overlapping sequence was used to confirm the full length clone. The full length protein sequence of human ADAMTS-9 is shown in Figure 29. The 5' end of the clone contains a methionine codon within a good Kozak consensus for translation initiation. A signal peptide sequence is located just downstream of this methionine in the translated ORF, and the size of the pro-domain is similar to that of other ADAM-TS family members. Therefore, this appears to be the starting methionine of ADAMTS-9.

The overall protein sequence of ADAMTS-9 is similar to that of the other ADAM-TS proteins. All of these family members have a pro-domain, metalloprotease domain, disintegrin-like domain, thrombospondin domain, spacer region, and a variable number of a thrombospondin-like submotifs at the carboxyl-terminal end of the protein (Figure 32A). Like other ADAM-TS family members, ADAMTS 9 contains an amino-terminal signal peptide sequence and lacks a transmembrane domain.

Among the 23 ADAM family members, 10 are predicted to be active proteases based on the sequence of their Zn binding catalytic sites (Black and White, *Curr. Opin. Cell. Biol* 10:654-659, 1998). The consensus catalytic sequence site based on ADAM and snake venom metalloproteases is HEXGHXXGXXHD (SEQ ID NO:51). The ADAM-TS family of proteins has homology to this consensus sequence except at the second conserved glycine. ADAMTS 9 has an asparagine at this conserved glycine site in the helix. Two other ADAM-TS proteins, ADAMTS-1 and ADAMTS-4, also have an asparagine in this position instead of glycine (Figure 32B). This suggests that ADAMTS-9, line ADAMTS-1 and ADAMTS-4, may have an active metalloprotease domain.

It has been proposed that an invariant cysteine residue in the pro-domain of MMP and ADAM proteins coordinates the catalytic Zn ion in the metalloprotease domain, thus maintaining the protease in an inactive state (Loechel et al., *J. Biol Chem.* 274:13427-33, 1999). Once the pro-domain is cleaved this interaction is interrupted and the protease is activated by a "cysteine switch" mechanism. A proposed cysteine switch

residue in ADAMTS-9 is marked in Figure 29 by a star. Proteolytic processing of the pro-domain of ADAM and ADAM-TS proteins is believed to occur by furin endopeptidases in the Golgi. ADAMTS-9 contains two potential furin cleavage sites (consensus RX(K/R)R; SEQ ID NO:35) at the end of the pro-domain (see Figure 29).
5 Based on the sequence of mature murine *ADAMTS-1*, the second furin cleavage site is most likely used in ADAMTS-9 (resulting amino-terminus FLSYPR).

Following the metalloprotease domain, ADAMTS-9 contains a cysteine-rich region that has homology to the disintegrin domain in snake venom metalloprotease and ADAMs. Next, all of the ADAM-TS family members contain an
10 internal TSP1 motif that has the two conserved heparin binding segments: W(S/G)XWSXW (SEQ ID NO:36) and CSVTCG (SEQ ID NO:37). Separating the internal TSP1 motif and the carboxy terminal TSP1-like submotifs is a variable length spacer region. As seen in Figure 32A, most ADAM-TS family members have between one and three TSP1-like submotifs at the end of the protein. However at the extremes
15 are ADAMTS 3 which has no TSP1-like motifs and *C. elegans* GON-1 which has 17 of these motifs. ADAMTS-9 contains one internal TSP1 motif and three TSP-1 like submotifs at the carboxyl end (Figure 30A). A possible role for ADAMTS 9 in the adult is suppression of angiogenesis through the carboxy-terminal TSP1 motifs.

Overall, the predicted mature forms of the ADAM-TS proteins show 20-
20 40% similarity to each other. Interestingly, by BLAST analysis ADAMTS-9 shows as much homology to *C. elegans* GON-1 as to other human ADAM-TS, suggesting that ADAMTS 9 may be the human homologue of GON-1. The dendrogram in Figure 30C (prepared with the MegAlign program (DNASar)) shows the relationship between the known human ADAM-TS members, ADAMTS 9, and GON-1.

25 The expression pattern of ADAMTS 9 was examined in a variety of human adult and fetal tissues using RT-PCR. For tissue distribution analysis, human multiple tissue cDNA panels I and II were purchased from Clontech. RT-PCR was performed using a touchdown procedure where the annealing temperature was dropped from 63°C to 57°C over 10 cycles then kept at 57°C for 20 cycles. The sense primer
30 was CAGGGGAAACAGACGATGACAAC (SEQ ID NO:38) and the antisense

primer was TGCGGTAACCCAAGCCACACT (SEQ ID NO:39). Expected product size was 510 bp. Control primers to glyceraldehyde-3-phosphate dehydrogenase (G3PDH) were supplied by Clontech--expected size is about 1 kb.

As seen with other ADAM-TS genes, Northern blot analysis showed
5 very low levels of expression. Therefore a more sensitive RT-PCR procedure was used. The cDNA panels used were normalized to the mRNA expression levels of several different housekeeping genes to ensure accurate assessment of tissue specificity. ADAMTS-9 was found in ovary, pancreas, heart, kidney, lung, placenta, and strikingly in all fetal tissues examined (Figure 31), suggesting a possible role in development. In
10 addition, using hybridization to cDNA libraries we have identified ADAMTS-9 in adult spinal cord and brain. However, ADAMTS-9 was not detected in colon, leukocyte, prostate, small intestine, testis, liver, skeletal muscle, spleen or thymus (Figure 31). Expression of the G3PDH housekeeping gene in all cDNAs tested is shown as a control for template integrity and the RT-PCR procedure. One notable difference in the
15 expression pattern of ADAMTS-9 compared to other ADAMTS genes is the presence of ADAMTS-9 in the adult kidney. This is of interest since the chromosomal locus containing ADAMTS-9 is often deleted in renal tumors.

A genomic clone of ADAMTS 9 was obtained by screening a human P1 library and used for FISH analysis (Genome Systems). Briefly, the human ADAMTS-9
20 genomic clone was labeled with digoxigenin dUTP by nick translation. Labeled probe was combined with sheared human DNA and hybridized to normal metaphase chromosomes derived from PHA stimulated peripheral blood lymphocytes in a solution containing 50% formamide, 10% dextran sulfate and 2X SSC. Specific hybridization signals were detected by incubating the hybridized slides in fluoresceinated
25 antidigoxigenin antibodies followed by counterstaining with DAPI for one-color experiments. Probe detection for two-color experiments was accomplished by incubating the slides in fluoresceinated antidigoxigenin antibodies and Texas red avidin followed by counterstaining with DAPI. A total of 80 metaphase cells were analyzed with 70 exhibiting specific labeling. Initial FISH experiments resulted in specific
30 labeling of the short arm of chromosome 3. Measurement of 10 specifically labeled

chromosome 3's demonstrated that ADAMTS-9 is located at a position which is 30% the distance from the centromere to the telomere of chromosome arm 3p, an area which corresponds to 3p14.3-21.1 (Figures 32A and 32B). Since deletions and other rearrangements of this locus are frequent and early events in the pathogenesis of a number of human cancers (including renal cell carcinoma, breast cancers, uterine cervical carcinoma and vulvar carcinomas, this region may contain one or more tumor suppressor genes.

The chromosomal localization of the human ADAMTS 9 locus was independently confirmed by PCR analysis of the Stanford G3 radiation hybrid mapping panel. The G3 hybrid mapping panel (Stewart et al., *Genomic Res.* 7:422-433, 1997) containing 83 radiation hybrid DNA, as well as human and hamster control DNAs was obtained from Research genetics Inc. (Huntsville, Alabama). The human chromosome content of each somatic cell hybrid was established by the Stanford Human Genome Center using more than 10,000 STSs derived from random genetic markers and expressed tagged sequences (<http://www-shgc.stanford.edu/Mapping/rh/>). PCR reactions were carried out in a 10 µl reaction volume containing 25 ng DNA template, 25 µm deoxynucleotide triphosphates, 20 pmol of each oligonucleotide primer, 0.5 U of Taq polymerase (Boehringer Mannheim), 2.5 mM MgCl₂, 50 mM KCl and 10 mM Tris-HCl (pH 8.3). The sense primer is GTGCGCTGGGTCCCTAAATAC (SEQ ID NO:40) which is in the coding sequence and the antisense primer is AAAATCACAGGTTGGCAGCGG (SEQ ID NO:41) which is in an intronic sequence. Thirty cycles of PCR were performed. Ten cycles consisted of denaturing at 94°C for 15 seconds, annealing at 62°C for 30 seconds, going down 0.5°C each cycle and extension at 72°C for 30 seconds. Twenty more cycles were performed using the same denaturing and extension conditions and keeping the annealing at 57°C for 30 seconds. PCR was proceeded by a 2 min incubation at 94°C and followed by a 72°C final soak for 10 minutes. Amplified products were electrophoresed through a 2% agarose gel and visualized by ethidium bromide staining. The resulting PCR product was a 302 bp human specific fragment. The presence or absence of the ADAMTS 9 product was scored for each of the somatic cell hybrids. The results were submitted to the Stanford

Radiation Hybrid Server via the internet (<http://www-shgc.stanford.edu>) and the completed data were returned to us. ADAMTS 9 was linked to the ordered markers SHGC-33668 with a LOD score of 11.47 and SHGC-20118 (D3S3571) with a LOD score of 11.06. The results confirm localization of ADAMTS 9 to the short arm of chromosome 3 and place ADAMTS-9 within the context of established maps. Furthermore SHGC-20118 (D3S3571) has been mapped to 3p14.2, placing ADAMTS-9 closer to the 14.2-14.3 region of chromosome 3. This location is interesting in that it contains a well characterized breakpoint for translocations common in hereditary renal cell carcinomas.

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From the foregoing, it will be appreciated that, although specific embodiments of the invention have been described herein for the purpose of illustration, various modifications may be made without deviating from the spirit and scope of the invention. Accordingly, the present invention is not limited except as by the appended claims.

15

CLAIMS

1. An isolated polynucleotide that encodes an ADAMTS polypeptide, wherein the polypeptide comprises:
 - (a) at least 50 consecutive amino acid residues of an ADAMTS protein that comprises a sequence recited in any one of SEQ ID NOs:2, 4, 10, 14, 16, 18, 22, 24, 26 or 27; or
 - (b) a variant of any of the foregoing amino acid sequences that differs in one or more substitutions, deletions, additions and/or insertions, wherein substitutions, if any, are present at no more than 10% of the consecutive residues of the ADAMTS protein.
2. A polynucleotide according to claim 1, wherein the polynucleotide comprises a sequence recited in any one of SEQ ID NOs:1, 3, 9, 13, 15, 17, 21, 23 or 25.
3. A polynucleotide according to claim 1, wherein substitutions, if any, are present at no more than 5% of the consecutive residues of the ADAMTS protein.
4. A polynucleotide according to claim 1, wherein the polypeptide has an ADAMTS activity that is not substantially diminished relative to the ADAMTS protein.
5. A recombinant expression vector comprising a polynucleotide according to claim 1.
6. A host cell transformed or transfected with an expression vector according to claim 5.
7. An isolated antisense polynucleotide complementary to at least 20 consecutive nucleotides present within a polynucleotide according to claim 1.

8. A method for preparing an ADAMTS polypeptide, the method comprising:

(a) culturing a host cell transformed or transfected with an expression vector comprising a polynucleotide that encodes an ADAMTS polypeptide comprising:

(i) at least 50 consecutive amino acid residues of an ADAMTS protein that comprises a sequence recited in any one of SEQ ID NOs:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26 or 27; or

(ii) a variant of any of the foregoing amino acid sequences that differs in one or more substitutions, deletions, additions and/or insertions, wherein substitutions, if any, are present at no more than 10% of the consecutive residues of the ADAMTS protein;

wherein the step of culturing is performed under conditions promoting expression of the polynucleotide sequence; and

(b) recovering an ADAMTS polypeptide.

9. A method for preparing an ADAMTS polypeptide, the method comprising:

(a) culturing a host cell according to claim 6 under conditions promoting expression of the polynucleotide; and

(b) recovering an ADAMTS polypeptide.

10. An isolated ADAMTS polypeptide comprising:

(a) at least 50 consecutive amino acid residues of an ADAMTS protein that comprises a sequence recited in any one of SEQ ID NOs:2, 4, 10, 14, 16, 18, 22, 24, 26 or 27; or

(b) a variant of any of the foregoing amino acid sequences that differs in one or more substitutions, deletions, additions and/or insertions, wherein substitutions, if any, are present at no more than 10% of the consecutive residues of the ADAMTS protein.

11. An ADAMTS polypeptide according to claim 10, wherein the polypeptide has an ADAMTS activity that is not substantially diminished relative to the ADAMTS protein.

12. A polypeptide comprising an amino acid sequence recited in any one of SEQ ID NOs:2, 4, 10, 14, 16, 18, 22, 24, 26 or 27.

13. An isolated ADAMTS polypeptide comprising:

(a) at least 50 consecutive amino acid residues of an ADAMTS protein that comprises a sequence recited in any one of SEQ ID NOs:6, 8, 12, or 20

(b) a variant of any of the foregoing amino acid sequences that differs in one or more substitutions, deletions, additions and/or insertions, wherein substitutions, if any, are present at no more than 10% of the consecutive residues of the ADAMTS protein.

14. An ADAMTS polypeptide according to claim 13, wherein the polypeptide has an ADAMTS activity that is not substantially diminished relative to the ADAMTS protein.

15. An ADAMTS polypeptide according to claim 13, wherein the polypeptide comprises at least 40 consecutive amino acid residues of an ADAMTS protein that comprises a sequence recited in any one of SEQ ID NOs:6, 8, 12, or 20.

16. A polypeptide comprising an amino acid sequence recited in any one of SEQ ID NOs:6, 8, 12, or 20.

17. A pharmaceutical composition comprising:

(a) an ADAMTS polypeptide comprising:

(i) at least 50 consecutive amino acid residues of an ADAMTS protein that comprises a sequence recited in any one of SEQ ID NOs: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26 or 27; or

(ii) a variant of any of the foregoing amino acid sequences that differs in one or more substitutions, deletions, additions and/or insertions, wherein substitutions, if any, are present at no more than 10% of the consecutive residues of the ADAMTS protein; and

(b) a physiologically acceptable carrier.

18. A vaccine comprising:

(a) an ADAMTS polypeptide comprising:

(i) at least 50 consecutive amino acid residues of an ADAMTS protein that comprises a sequence recited in any one of SEQ ID NOs:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26 or 27; or

(ii) a variant of any of the foregoing amino acid sequences that differs in one or more substitutions, deletions, additions and/or insertions, wherein substitutions, if any, are present at no more than 10% of the consecutive residues of the ADAMTS protein; and

(b) a non-specific immune response enhancer.

19. An isolated antibody, or antigen-binding fragment thereof, that specifically binds to an ADAMTS polypeptide that comprises a sequence recited in any one of SEQ ID NOs: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26 or 27.

20. A method for screening for an agent that modulates ADAMTS protein expression in a cell, comprising:

(a) contacting a candidate modulator with a cell expressing an ADAMTS polypeptide, wherein the polypeptide comprises:

(i) at least 50 consecutive amino acid residues of an ADAMTS protein that comprises a sequence recited in any one of SEQ ID NOs:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26 or 27; or

(ii) a variant of any of the foregoing amino acid sequences that differs in one or more substitutions, deletions, additions and/or insertions, wherein

substitutions, if any, are present at no more than 10% of the consecutive residues of the ADAMTS protein; and

(b) subsequently evaluating the effect of the candidate modulator on expression of an ADAMTS mRNA or polypeptide, and therefrom identifying an agent that modulates ADAMTS protein expression in the cell.

21. A method for screening for an agent that modulates an ADAMTS protein activity, comprising:

(a) contacting a candidate modulator with an ADAMTS polypeptide, comprising:

(i) at least 50 consecutive amino acid residues of an ADAMTS protein that comprises a sequence recited in any one of SEQ ID NOs:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26 or 27; or

(ii) a variant of any of the foregoing amino acid sequences that differs in one or more substitutions, deletions, additions and/or insertions, wherein substitutions, if any, are present at no more than 10% of the consecutive residues of the ADAMTS protein;

wherein the polypeptide has an ADAMTS activity that is not substantially diminished relative to the ADAMTS protein;

and wherein the step of contacting is carried out under conditions and for a time sufficient to allow the candidate modulator to interact with the polypeptide; and

(b) subsequently evaluating the effect of the candidate modulator on an ADAMTS activity of the polypeptide, and therefrom identifying an agent that modulates an activity of an ADAMTS protein.

22. An agent that decreases expression or activity of an ADAMTS protein that comprises a sequence recited in any one of SEQ ID NOs:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26 or 27, for use in the manufacture of a medicament for inhibiting neuroinflammation in a patient.

23. An agent according to claim 22, wherein ADAMTS activity is decreased by inhibiting expression of an endogenous ADAMTS gene.

24. An agent according to claim 22, wherein ADAMTS activity is decreased by administering a modulating agent that binds to an ADAMTS protein.

25. An agent that decreases expression or activity of an ADAMTS protein that comprises a sequence recited in any one of SEQ ID NOs:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26 or 27, for use in the manufacture of a medicament for inhibiting neurodegeneration in a patient.

26. An agent according to claim 25, wherein ADAMTS activity is decreased by inhibiting expression of an endogenous ADAMTS gene.

27. An agent according to claim 25, wherein ADAMTS activity is decreased by administering a modulating agent that binds to an ADAMTS protein.

28. A pharmaceutical composition according to claim 17, for use in the manufacture of a medicament for method for treating a patient afflicted with a condition associated with neuroinflammation and/or neurodegeneration.

29. A composition according to claim 28, wherein the condition is selected from the group consisting of Alzheimer's disease, Parkinson's disease and stroke.

30. A method for modulating ADAMTS activity in a cell, comprising contacting a cell expressing an ADAMTS polypeptide with an effective amount of an agent that modulates ADAMTS protein activity or expression, wherein the ADAMTS polypeptide comprises:

(i) at least 50 consecutive amino acid residues of an ADAMTS protein that comprises a sequence recited in any one of SEQ ID NOs:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26 or 27; or

(ii) a variant of any of the foregoing amino acid sequences that differs in one or more substitutions, deletions, additions and/or insertions, wherein substitutions, if any, are present at no more than 10% of the consecutive residues of the ADAMTS protein;

wherein the polypeptide has an ADAMTS activity that is not substantially diminished relative to the ADAMTS protein;

and thereby modulating ADAMTS activity in the cell.

31. A pharmaceutical composition according to claim 17, for use in the manufacture of a medicament for treating a patient afflicted with a condition associated with cell proliferation, cell migration, inflammation and/or angiogenesis.

32. A composition according to claim 31, wherein the condition is selected from the group consisting of cancer, arthritis and autoimmune diseases.

33. An agent that decreases expression or activity of an ADAMTS protein that comprises a sequence recited in any one of SEQ ID NOs:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26 or 27, for use in the manufacture of a medicament for treating a patient afflicted with an invasive tumor.

34. An agent that decreases expression or activity of an ADAMTS protein that comprises a sequence recited in any one of SEQ ID NOs:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26 or 27, for use in the manufacture of a medicament for treating a patient afflicted with a brain tumor.

35. An agent that decreases expression or activity of an ADAMTS protein that comprises a sequence recited in any one of SEQ ID NOs:2, 4, 6, 8, 10, 12, 14, 16, 18, 20,

22, 24, 26 or 27, for use in the manufacture of a medicament for treating a patient afflicted with a brain injury.

36. An agent according to any one of claims 33-35, wherein the ADAMTS protein comprises a sequence recited in SEQ ID NO:16.

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AGGACCAAGCGGTTTGTGTCTGAGGCGCGCTTCGTGGAGACGCTGCTGGTGGCCGATGCGTCCATGGCTGCCTTCTACGG
GGCCGACCTGCAGAACCACATCCTGACGTTAATGTCTGTGGCAGCCCGAATCTACAAGCACCCAGCATCAAGAATTCCA
TCAACCTGATGGTGGTAAAAGTGCTGATCGTAGAAGATGAAAAATGGGGCCAGAGGTGTCCGACAATGGGGGGCTTACA
CTGCGTAACCTTCTGCAACTGGCAGCGGCGTTTCAACCAGCCAGCGACCGGCACCCAGAGCACTACGACACGGCCATCCT
GCTCACCAGACAGAATTCTGTGGGCAGGAGGGGCTGTGTGACACCTGGGTGTGGCAGACATCGGGACCATTGTGTACC
CCAACAAAAGCTGCTCCGTGATCGAGGATGAGGGGCTCCAGGCGGCCACACCCTGGCCCATGAACTAGGGCACGTCTC
AGCATGCCCCACGACGACTCCAAGCCCTGCACACGGCTCTTCGGGCCCATGGGCAAGCACCACTGATGGACCGCTGTT
CGTCCACCTGAACCAGACGCTGCCCTGGTCCCCCTGCAGCGCCATGTATCTCACAGAGCTTCTGGACGGCGGGCACGGAG
ACTGTCTCCTGGATGCCCCTGCTGGGCCCTGCCCTCCCCACAGGCTCCCGGGCCGCATGGCCCTGTACCAGCTGGAC
CAGCAGTGCAGGCAGATCTTTGGGCGGATTTCCGCCACTGCCCAACACCTCTGCTCAGGACGTCTGCCCCAGCTTTG
GTGCCACACTGATGGGGCTGAGCCCTGTGCCACACGAAGAATGGCAGCCTGCCCTGGGTGACGGCACGCCGTGCGGGC
CTGGGCACCTCTGCTCAGAAGGCAGCTGTCTACCTGAGGAGGAAGTGGAGAGGCCCAAGCCGTTGGTAGATGGAGGCTGG
GCACCGTGGGACCTCGGGGAGAATGTTCTCGGACCTGTGGAGGAGGAGTACAGTTTTACACCGTGAGTGAAGGACCC
CGAGCCTCAGAATGGAGGAAGATACTGCCTGGGTGGAGAGCCAAGTACCAGTCATGCCACACGGAGGAATGCCCCCTG
ACGGGAAAAGCTTACGGGAGCAGCAGTGTGAGAAGTATAATGCCTACAATTACACTGACATGGACGGGAATCTCTGCAG
TGGGTCCCCAAGTATGCTGGGGTGTCCCCCGGGACCGCTGCAAGTTGTTCTGCCGAGCCCGGGGAGGAGCGAGTTCAA
AGTGTTGAGGCCAAGGTGATTGATGGCACCTGTGTGGGCCAGAAACACTGGCCATCTGTGTCCGTGGCCAGTGTGTCA
AGGCCGGCTGTGACCATGTGGTGGACTCGTTTTGGAAGCTGGACAAATGCGGGGTGTGTGGGGGAAAGGCAACTCCTGC
AGGAAGGGCTCCGGGTCCCTCACCCCAACCAATTATGGCTACAATGACATTGTACCATCCAGCTGGTGCCACTAATAT
TGACGTGAAGCAGCGGAGCCACCCGGGTGTGCAGAACGATGGGAACCTACCTGGCGCTGAAGACGGCTGATGGGCAGTACC
TGCTCAACGGCAACCTGGCCATCTCTGCCATAGAGCAGGACATCTTGGTGAAGGGGACCATCCTGAAGTACAGCGGCTCC
ATCGCCACCTGGAGCGCTGCAGAGCTTCGGGCCCTTGCCAGAGCCTCTGACAGTGCAGCTCCTGGCAGTCCCTGGCGA
GGTCTTCCCCCAAAAGTCAAATACACCTTCTTTGTTCCTAATGACGTGGACTTTAGCATGCAGAGCAGCAAAGAGAGAG
CAACCACCAACATCACCCAGCCGCTGCTCCACGCACAGTGGGTGCTGGGGGACTGGTCTGAGTGCTCTAGCACCTGCGGG
GCCGGCTGGCAGAGGCGAACTGTAGAGTGCAGGGACCCCTCCGGCCAGGCCTCTGCCACCTGCAACAAGGCTCTGAAACC
CGAGGATGCCAAGCCCTGCGAAAGCCAGCTGTGCCCCCTGTGATTCAAGGGGGCAGGGGCCAGTCTTGTGCTCCTGGACA
TGCGGTACTGAGGTGCAGACAAGGTCTCCACTGTGGTGAAGTGGTCCCTTGCCCATATCAAGGCAGCACGGCCACCCA
GGCCTCCCATTGCCGCAACCCCTCCAGTACTGCACAAATTCCTAAGGGGAAGAGGAGAGGGTATGGGGCGGCAGACCCT
ATCATCACTGTCCAGTGGACTGGACCTTGCTCGGGTTCAAGTAGAGGGCATAGGTTAAAAGGTAAAAGTGCACCTATTG
TACCAGACAGGACGCCCCGGAATTC

Fig. 1

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RTKRFVSEARFVETLLVADASMAAFYGADLQNHILTLMSVAARIYKHPSIKNSINLMVVKVLIVEDEKWGPEVSDNGGLT
LRNFCNWQRRFNQPSDRHPEHYDTAILLTRQNFCGQEGLCDTLGVADIGTICDPNKSCSVIEDEGLQAAHTLAHELGHVL
SMPHDDSKPCTRLFPGMGKHHVMAPLFVHLNQTLPWSPCSAMYLTELLDGGHGDCLLDAPAAALPLPTGLPGRMALYQLD
QQCRQIFGPDFRHCNNTSAQDVCAQLWCHTDGAEPLCHTKNGSLPWADGTPCGPGHLCSEGSCLPEEEVERPKPVVDGGW
APWGPWGECSRTCGGGVQFSHRECKDPEPQNGGRYCLGRRAKYQSCHEECPPDGKSFREQQCEKYNAYNYTMDGNLLQ
WVPKYAGVSPDRCKLFCRARGRSEFKVFEAKVIDGTLCPETLAICVRGQCVKAGCDHVVDSEFKLDCGVCVGGKGNCS
RKGSGSLTPTNYGYNDIVTIPAGATNIDVKQRSHPGVQNDGNYLALKTADGQYLLNGNLAISAEQDILVKGTILKYSGS
IATLERLQSFRLPEPLTVQLLAVPGEVFPKVKYTFVPNDVDFSMQSSKERATTNITQPLLHAQWVLGDWSECSSTCG
AGWQRRTVECRDPSGQASATCNKALKPEDAKPCESQLCPL.

Fig. 2

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CCCCCCTCGAGGTCGACGGTATCGATAAGCTTGATATCGAATTCGGGGCCCCCACCCTCGCCCTGAAACTTCTATAG
CAAATAGCAAACATCCAGCTAGACTCAGTCGCGCAGCCCTCCCGCGGGCAGCGCACTATGCGGCTCGAGTGGGCGTCC
TTGCTGCTGCTACTGCTGCTGCTGTGCGCGTCTGCCTGGCCCTGGCCGCTGACAACCTGCCGCGGCACCTGCCAGGA
TAAACCAGGCAGCCTCGGGTCTGTCAGCGGCTGCCAGCCGACCAGCGGCAGTGGGAGGAAACACAGGAGCGGGGCC
ATCTGCAACCTTGGCCAGGCAGCGCAGGAGCAGCGGGTGGTGCAGAATATAGACCAACTCTACTCTGGCGGTGGCAA
GTGGGCTACCTTGTCTACGCGGGCGGCCGGAGGTTCTGCTGGACCTGGAGAGGGATGACACAGTGGGTGCTGCTGGTGG
CATCGTTACTGCAGGAGGGCTGAGCGCATCTCTGGCCACAGGGTCACTGCTTCTACAGAGGCACCTGTGGACGCGAGCC
CTCGATCCCTAGCTGTCTTTGACCTCTGTGGGGTCTCGATGGCTTCTTCGAGTCAAGCATGCGCGCTACACTCTGAGG
CCGCTCTTGGTGGGTCTGGGCGAGTCCGAACGAGTTACGGGGATGGGTCTTACGCATCTGTCATGTCTACACCCG
CGAGGGCTTCAGCTTCGAGGCCTGCCGCCACGCACCAAGTTGCGAGACTCCAGCGTCCCGTCTGGGGCCCAAGAGAGCC
CCTCGGTGCACAGTAGTTCTAGGCGACGCACAGAAGTGGACCGCAGCTGCTGGACCATTAGCTTTCTGCCAGCTGGG
AACGCGGGACCTCAGACCTGGTGGAGGCGGAGCGCGCTTCCATCTCCAGGGCCCGCAGGTGGAGCTCCTCTTGGTGGC
TGACTCTTCATGGCCAAGATGTATGGGCGGGCCTGCAGCATTACCTGCTGACCCTGGCCTCTATTGCCAACCGGCTGT
ACAGTCATGCAAGCATCGAGAACCACATCCGCTGGCCGTAGTGAAAGTGGTGGTGTGACCGACAAGAGTCTGGAGGTG
AGCAAGAACGCGGCCACGACCTCAAGAACTTTGCAATGGCAGCACCAACACAACCAGCTAGGTGATGACCATGAGGA
GCACTACGATGCAGCCATCCTGTTACCCAGAGAGGATTTATGTGGGCATCATTATGTGACACCCTGGGAATGGCAGCG
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Fig. 3A

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TGTACAAAGATTATCGGAACCTTCAATAAAAAAGCAAGGGTTATACTGACGTTGTGAGGATCCCTGAAGGAGCAACCCA
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Fig. 3B

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Fig. 4

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KIAA0605 Accession #: AB011177

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Fig. 5A

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Fig. 5B

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 GTDIVRGCDPLVKPVGRQACDLQPCPTEPPDDSCDQDQPGTNCALAIKVNLCGHMYSKACCRSCRPPHS (951 amino acids)

Fig. 6

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DNA sequence of metalloproteinase gene (KIAA0366) Accession #: AB002364

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Fig. 7A

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Fig. 7B

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Fig. 7C

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 psrslenvcrwasqqqrsdlnhsehdhaifltrqdfgpagmqgyapvtgmchpvrscnlhedgfssafvvahtghvl
 gmehdgggnrcgdetamgsmaplvqaaafhryhwsrscgqelkryihsydclddpfdhdwplpelpginysmdeqcrf
 dfvgvykmctaftrfdpckqlwchshpndpyfcktkkgppldgtecaagkwcyghcmwknanqqkqdgngswtkfgscs
 rtcgtgvrfrtrqcnmpingggdcpgvnfeyqlcnteecqkhfedfraqqcqqrnshfeyqntkhhwlpvehdpdkkr
 chlycqskegdvaymkqlvhdgthcsykdpysicvrgecvkvgcdkeigsnkvedkcgvcggnshcrtvkgfttrtp
 klgylnmfdippgarinvliqedasphilaiknqatghylngkgeeaksrftidlgewdynieddieslhtdgpldp
 vivliipqendrssltykiihedsvptinsnviqeeidt fewalkswsqvskpcgggfytkygcrrksdnkmvnr
 fceankkpkpirmcniqecthplwaeewehctktcgssgyqlrtvrcqlplldgtnrsvhskycmgdrpesrrpcnrv
 pcpaqwktpwsecsvtcgegtvrqvlcragdhcdgekpesvracqlppcndepclgdksifcomevlarycsipgynk
 lccescskrsstlpppyllaethddvisnpsdlprslvmptslvpyhsetpakkmslssissvggnayaafrpnskp
 dganlqrsaqqagsktvrlvtvpsspptkrvhlssasqmaasffaasdsigassqartskkdgiidnrrptrsstle
 r (1.201)

Fig. 8

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GGAATTCGCGGCCGCGTCGACGTCAATACCAACTCCGAGCACACGGCCGTCATCAGCCTCTGCTCAGGAATGCTGGGCAC
ATTCCGGTCTCATGATGGGATTATTTTATTGAACCACTACAGTCTATGGATGAACAAGAAGATGAAGAGGAACAAAACA
AACCCACATCATTTATAGGCGCAGCGCCCCAGAGAGAGCCCTCAACAGGAAGGCATGCATGTGACACCTCAGAACAC
AAAAATAGGCACAGTAAAGACAAGAAGAAAACCAGAGCAAGAAAATGGGGAGAAAGGATTAACCTGGCTGGTGACGTAGC
AGCATTAAACAGCGGCTTAGCAACAGAGGCATTTTCTGCTTATGGTAATAAGACGGACAACACAAGAGAAAAGAGGACCC
ACAGAAGGACAAAACGTTTTTATCCTATCCACGGTTTGTAGAAGTCTTGGTGGTGGCAGACAACAGAATGGTTTCATAC
CATGGAGAAAACCTTCAACACTATATTTAACTTTAATGTCAATTGATGGGCCTTCCATATCTTTAATGCTCAGACAAC
ATTAACAAACCTTTGCCAGTGGCAGCATTGAAGAAGTCCAGGTGGAATCCATCATGATACTGCTGTTCTCTTAACAA
GACAGGATATCTGCAGAGCTCAGACAAATGTGATACCTTAGGCCTGGCTGAAGTGGGAACCATTTGTGATCCCTATAGA
AGCTGTTCTATTAGTGAAGATAGTGGATTGAGTACAGCTTTTACGATCGCCCATGAGCTGGGCCATGTGTTTAACATGCC
TCATGATGACAACAACAAATGTAAAGAAGAAGGAGTTAAGAGTCCCAGCATGTCATGGCTCCAACACTGAACTTCTACA
CCAACCCCTGGATGTGGTCAAAGTGTAGTCGAAAATATATCACTGAGTTTTTAGACACTGGTTATGGCGAGTGTTTGCTT
AACGAACCTGAATCCAGACCCCTACCTTTGCCTGTCCAAGTCCAGGCATCCTTTACAACGTGAATAAACAATGTGAATT
GATTTTGGACAGGTTCTCAGGTGTGCCATATATGATGCAGTGCAGACGGCTCTGGTGCAATAACGTCAATGGAGTAC
ACAAAGGCTGCCGACTCAGCACACCCCTGGGCCGATGGGACGAGTGCAGCCTGGAAGCACTGCAAGTATGGATT
TGTGTTCCCAAAGAAATGGATGTCCCCGTGACAGATGGATCCTGGGAAGTTGGAGTCCCTTTGGAACCTGCTCCAGAAC
ATGTGGAGGGGCATCAAAACAGCCATTGAGAGTGAACAGACCAGAACCAAAAATGGTGGAAAATACTGTGTAGGAC
GTAGAATGAAATTTAAGTCTGCAACACGGAGCCATGTCTCAAGCAGAAGCGAGACTTCCGAGATGAACAGTGTGCTCAC
TTTGACGGGAAGCATTTTAACATCAACGGTCTGCTTCCCAATGTGCGTGGTCCCTAAATACAGTGGAACTCTGATGAA
GGACCGGTGCAAGTTGTTCTGCAGAGTGGCAGGGAACACAGCCTACTATCAGCTTGCAGACAGAGTGATAGATGGAACCTC
CTTGTTGCCAGGACACAAATGATATCTGTGTCCAGGGCCTTTGCCGCAAGCTGGATGCGATCATGTTTTAACTCAAAA
GCCCCGAGAGATAATGTGGGTTTGTGGTGGCGATAATTCTTCATGCAAAACAGTGGCAGGAACATTTAATACAGTACA
TTATGGTTACAATACTGTGGTCCGAATTCAGCTGGTGTACCAATATTGATGTGCGGCAGCACAGTTTCTCAGGGGAAA
CAGACGATGACAACTACTTAGCTTTATCAAGCAGTAAAGGTGAATTCTTGCTAAATGGAACTTTGTTGTCACAATGGCC
AAAAGGGAATTCGCATTGGGAATGCTGTGGTAGAGTACAGTGGTCCGAGACTGCCGTAGAAAGAATTAACCAACAGA
TCGATTGAGCAAGAATTTTGCTTCAGGTTTTGTCGGTGGGAAAGTTGTACAACCCGATGTACGCTATTCTTTCAATA
TTCCAATTGAAGATAAACCTCAGCAGTTTTACTGGAACAGTCATGGCCATGGCAAGCATGCAGTAAACCTGCCAAGGG
GAACGGAAACGAAAACCTGTTTGACCCAGGGAATCTGATCAGCTTACTGTTTCTGATCAAAGATGCGATCGGCTGCCCA
GCCTGGACACATTACTGAACCTGTGGTACAGACTGTGACCTGAGGTGGCATGTTGCCAGCAGGAGTGAATGTAGTGCCC

Fig. 9A

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AGTGTGGCTTGGGTACCGCACATTGGACATCTACTGTGCCAAATATAGCAGGCTGGATGGGAAGACTGAGAAGGTTGAT
 GATGGTTTTTGCAGCAGCCATCCCAAACCAAGCAACCGTGAAAAATGCTCAGGGGAATGTAACACGGGTGGCTGGCGCTA
 TTCTGCCTGGACTGAATGTTCAAAAAGCTGTGACGGTGGGACCCAGAGGAGAAGGGCTATTTGTGTCAATACCGGAAATG
 ATGTACTGGATGACAGCAATGCACACATCAAGAGAAAGTTACCATTGAGAGGTGAGTGAGTTCCCTTGTCCACAGTGG
 AAATCTGGAGACTGGTCAGAGTGCTTGGTCACCTGTGAAAAGGGCATAAGCACCGCCAGGTCTGGTGTGAGTTTGGTGA
 AGATCGATTAAATGATAGAATGTGTGACCCAGAGGTGACGCGGCCGGAATTCGCCGATACTGACGGGCTCCAGGAGT
 CGTCGCCACCAATCCCATATGGAACCGTCGATATTCAGCCATGTGCCTTCAAGCCGAATTCAG

Fig. 9B

GIRGRVDVNTNSEHTAVISLCSGMLGTFRSHDGDYFIEPLQSMDEQEDEEEQNKPHEIYRRSAPQREPSTGRHACDTSEH
 KNRHSDKKKTRARKWGERINLAGDVAALNSGLATEAFSAYGNKTDNTREKRTHRRTRKFLSYPRFVEVLVVADNRMVSY
 HGENLQHYILTLMSIDGPSISFNAQTTLKNLCQWQHSKNSPGGIHHDVAVLLTRQDICRAHDKCDTLGLAELGTICDPYR
 SCSISEDGLSTAFTIAHELGHVFNMPHDDNNKCKEEGVKSPQHVMAPTLNFYTNPMMWSKCSRKYITEFLDTGYGECLL
 NEPESRPYPLPVQLPGILYNVNKQCELIFGPGSQVCPYMMQCRRLWCNNVNGVHKGCRTQHTPWADGTECEPGHKCKYGF
 CVPKEMDVPVTDGWSGWSFPGTCSRTCGGGIKTAIRECNRPKNGGKYCVGRMKFKSCNTEPCLKQKRDFRDEQCAH
 FDGKHFNINGLLPNVRWVPKYSGILMKDRCKLFCRVAGNTAYYQLRDRVIDGTGCGQDTNDICVQGLCRQAGCDHVLNSK
 ARRDKCGVCGGDNSSCKTVAGTFNTVHYGYNTVVRIPAGATNIDVRQHSFSGETDDNYLALSSSKGEFLLNGNFVTMA
 KREIRIGNAVVEYSGSETAVERINSTDRIEQELLLQVLSVGKLYNPVRYSFNPIEDKPQQFYWNHGPWQACSKPCQG
 ERKRKLVTRESQQLTVSDQRCORLPQPGHITPCGTDCDLRWHVASRSECSAQCGLYRTLDIYCAKYSRLDGKTEKVD
 DGFCSHPKPSNREKCSGECNTGGWRYSAWTECSKCDGGTQRRRAICVNTRNDVLDOSKCTHQEKVTIQRCEFPQPQW
 KSGDWSECLVTCGKGHKHRQVWCQFGEEDRLNDRMCDPEVDAAANSADTDGLQESSPPIIWKPSIFSHVPSSRIP

Fig. 10

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cacatatgcacgagagagacagaggagaaagagacagagacaaaggcacagcggagaaggcagagacagggcaggcac
agaagcggcccagacagagtcctacagaggagagggcagagaagctgcagaagacacaggcaggagagacaaagatcc
aggaaaggagggtcaggaggagagtttgagaagccagaccctgggcacctctcccaagcccaaggactaagttttct
ccatttcctttaacggtcctcagcccttctgaaaactttgcctctgaccttggcaggagtccaagccccagggtacaga
gaggagctttccaaagctaggggtgtgaggacttggcgccctagacggcctcagtcctcccagctgcagtaccagtgcc
atgtcccagacaggctcgcatcccgggaggggcttggcagggcgctggctgtggggagcccaaccctgcctcctgctccc
cattgtgccgctctcctggctgggtgtggctgcttctgctactgctggcctctctcctgccctcagcccggtggccagcc
ccctccccgggaggaggagatcgtgttccagagaagctcaacggcagcgctcctgcctggctcgggcacccctgccagg
ctgtgtgccgcttgccagcccttggggagacgctgctactagagctggagcaggactccggtgtgcaggctcagggggt
gacagtgcagtacctgggcccaggcgcctgagctgctgggtggagcagagcctggcacctacctgactggcaccatcaatg
gagatccggagtcgggtggcatctctgactgggatgggggagccctgttaggcgtgttacaatatcggggggctgaactc
cacctccagccccggaggaggcaccctaactctgctgggggacctggggctcacatcctacgccggaagagtcctgc
cagcggtaagggtcccatgtgcaacgtcaaggctcctctggaagccccagccccagccccgaagagccaagcgcttgc
cttactgagtagatttgtggagacactgggtggcagatgacaagatggccgattccacggtgcggggctaaagcgc
tacctgctaacagtgatggcagcagcagccaaggccctcaagcaccgaagcatccgcaatcctgtcagcttgggtgtgac
tcggctagtatcctggggtcagcgaggaggggccccaaagtggggcccagtgctgccagaccctgcgcagcttctgtg
cctggcagcggggcctcaacaccctgaggactcggaccctgaccactttgacacagccattctgtttaccctcaggac
ctgtgtggagtctccacttgcgacacgctgggtatggctgatgtgggcaccgtctgtgaccggctcggagctgtgcat
tgtggaggatgatgggtccagtcagccttactgctgctcatgaactgggtcatgtcttcaacatgctccatgacaact
ccaagccatgcatcagtttgaatgggcctttgagcacctctcgccatgtcatggcccctgtgatggctcatgtggatcct
gaggagccctgggtccccctgcagtgcccgttcatcactgacttccctggacaatggctatgggactgtctcttagacaa
accagaggctccattgcatctgcctgtgactttccctggcaaggactatgatgctgaccgccagtgccagctgacctcg
ggcccgactcacgccattgtccacagctgccgccgcccgtgctgccctctgggtgcttggccacctcaatggccatgcc
atgtgccagacaaacactcgccctgggccgatggcacaccctgcgggcccgcacaggcctgcatgggtggctgctgcct
ccacatggaccagctccaggacttcaatatccacaggctgggtggctgggtccttggggaccatgggggtgactgctctc
ggacctgtgggggtgggtgtccagttctcctcccagactgcacgaggcctgtccccggaatgggtggcaagtactgtgag
ggccgcccgtaccgcttccgctcctgcaacactgaggactgccaactggctcagccctgaccttccgcgaggagcagtg
tgctgctacaaccaccgcaccgaccttccaagagcttccagggcccatggactgggttctcgcgtacacagggctgg
ccccccaggaccagtgcaaaactcacctgccaggccccggcactgggtactactatgtgctggagccacgggtggtagat

Fig. 11A

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gggacccccctgttccccggacagctcctcggctctgtgtccagggccgatgcatccatgctggctgtgatcgcatcattgg
ctccaagaagaagittgacaagtcatggtgtgcggaggggacggttctggttgacagcaagcagtcaggctccttcagga
aattcaggtacggatacaacaatgtggtcactatccccgcggggccaccacattcttgtccggcagcagggaaacctt
ggccaccggagcatctacttggccctgaagctgccagatggctcctatgccctcaatggtgaatacacgctgatgccctc
ccccacagatgtggtactgcctggggcagtcagcttgccgtacagcggggccactgcagcctcagagacactgtcaggcc
atgggccactggcccagcctttgacactgcaagtcctagtggctggcaacccccaggacacacgcctccgatacagcttc
ttcgtgccccggccgacccctcaacgccacgccccactccccaggactggctgcaccgaagagcacagattctggagat
ccttcggcggcggccctggggcggcaggaaataacctcactatccccggtgccctttctgggcaccggggcctcggaactt
agctgggagaaagagagagcttctgttgctgcctcatgctaagactcagtggggaggggctgtgggctgagacctgccc
ctcctctctgcciaatgcgcaggctggccctgccctgggttctcctggcctgggaggcagtgatgggttagtggaag
gggctgacagacagccctccatctaaactgccccctctgccctgcccgtcacaggaggaggagggaaggcaggaggggcc
tgggccccagttgcaattatttagtatttattcacttttatttagcaccagggaagggaacaaggactagggtcctgggg
aacctgacccctgacccctcatagccctcaccctggggctaggaaatccagggtggtggtgataggtataagtggtgtgt
gtatgctgtgtgtgtgtgtgtgaaatgtgtgtgtgtgtatgtatgaggtacaacctgttctgctttcctcttcctgaa
ttttattttttgggaaaagaaaagtcaagggtagggtgggcttcaggaggatgagggtattcttttttttttttcttt
ctttctttcttttttttttttgagacagaatctcgctctgtcgccaggctggagtgaatggcacaatctcggtcact
gcatcctccgctcccggttcaagtgttctcatgcctcagcctcctgagttagtggtggtattacaggctcctgccaccac
ggccagctaattttgtttgtttgtttgtttggagacagagtcctcgctattgtcaccagggtggaatgatttcagctcact
gcaaccttcgccacctgggttccagcaattctcctgcctcagcctcccagtagctgagattataggcacctaccaccac
ggccggctaattttgtatttttagtagagacggggttcaccatgttggccaggctggtctcgaactcctgacctagg
tgatccactcgcttcatctcccaaagtgtgggttacaggcgtgagccaccgtgcctggccacgcccactaattttt
gtatttttagtagagacagggtttcaccatgttggccaggctgctcttgaactcctgacctcaggtaatcgacctgcctc
ggcctcccaaagtgtgggttacagggtgtgagccaccacggcggtacatatatttttaaattgaattctactatttatg
tgatccttttgagtcagacagatgtggttgcatcctaactccatgtctctgagcattagatttctcatttgccaataat
aatacctcccttagaagttgtgtgaggattaaataatgtaaataaagaactagcataac

Fig. 11B

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MSQTGSHPGRGLAGRWLWGAQPCLLLPIVPLSWLVLLLLLLASLLPSARLASPLPREEEIVFPEKLNGSVLPGSGTPAR
LLCRLQAFGETLLLEEQDSGVQVEGLTVQYLGQAPELLGGAEPGYLTGTINGDPESVASLHWDGGALLGVLQYRGAE
HLQPLEGGTPNSAGGPGAHLRRKSPASGQGPCNVKAPLGSPSPRRRAKRFASLSRFVETLVVADDKMAAFHGAGLKR
YLLTVMAAAAKAFKHPsirNPVSLVVTSLVILGSGEEGPQVGPSAAQTLRSFCAWQRLNTPEDSDPDHFDTAILFTRQD
LCGVSTCDTLGMADVGTVCDPARSCAIVEDDGLQSAFTAAHELGHVFNMLHDNSKPCISLNGPLSTSRHVMApVMAHVDp
EEPWSPCSARFITDFLDNGYGHCLLDKPEAPLHLPVTFPGKDYDADQCQLTFGPDSRHCPQLPPPCAALWCSGHLNGHA
MCQTKHSPWADGTPCGPAQACMGGRCLEHMDQLQDFNIQAGGHWGPWGPWGDCSRTCGGGVQFSSRDCTRVPVPRNGGKYCE
GRRTRFRSCNTEDCPTGSALTFREEQCAAYNHRTDLFKSFPGPMDWVPRYTGVAPOQCKLTCQARALGYYYVLEPRVVD
GTPCSPDSSSVCVQGRCIHAGCDRIIGSKKKFDKCMVCGDGSKQSGSFRKFRYGYNVVTIPAGATHILVRQQGNP
GHRSIYLALKLPDGSYALNGEYTLMPSPDVLPGAVSLRYSGATAAETLSGHGPLAQPLTLQVLVAGNPQDTRLRYSF
FVPRPTPSTPRPTPQDLHRRRAQILEILRRRPWAGRK

Fig. 12

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Rat ADAMTS 5 DNA

ACTCACTATA GGGCTCGAGC GGCCGCCCGG GCAGGTCAGA GGCTCACTGG CAGCTCTCTA	60
GACCTGCGAC GCTGCTTCTA TTCCGGGTAT GTGAACGCGG AGCCAGACTC CTTTGCTGCT	120
GTAAGCCTAT GCGGGGGTCT CCGCGGAGCC TTGGGTACC AAGGTGCGGA GTATGTCATT	180
AGCCCTCTGC CCAACACCAG CGCGCCTGAG GCGCAGCGTC ATAGCCAGGG CGCACACCTT	240
CTCCAGCGCC GGGGTGCTCC CGTAGGGCCT TCCGGAGACC CTACCTCTCG CTGCGGGGTG	300
GCCTCGGGCT GGAACCCCGC CATCCTGAGG GCCTTGGACC CTTATAAACC ACGGCGGACG	360
GGCGTGGGCG AAAGCCACAA CCGGCGCAGG TCTGGGCGCG CCAAGCGCTT CGTGTCTATA	420
CCACGGTACG TGGAGACACT GGTGGTGGCG GACGAGTCAA TGGTCAAGTT TCACGGCGCG	480
GATTTGAAC ATTATCTGCT GACGCTGCTG GCCACGGCGG CGCGACTCTA CCGCCACCCC	540
AGCATCCTCA ACCCTATCAA CATCGTTGTG GTCAAGGTGT TACTCTTAGG AGATCGTGAC	600
ACTGGGCCCC AGGTCACAGG CAACGCGGCC CTGACTCTGC GCAACTTCTG TGCCTGGCAG	660
AAAAAGTTGA ACAAAGTGAG CGACAAGCAC CCCGAGTACT GGGACACAGC CATCCTCTTC	720
ACCAGACAGG ACCTATGCGG GGCTACCACC TGTGACACCT TGGGCATGGC TGATGTGGGC	780
ACCATGTGTG ATCCCAAGAG AAGCTGCTCT GTCATCGAGG ACGATGGGCT TCCGTCGGCC	840
TTCACCACTG CCCATGAGCT GGGCCATGTG TTCAACATGC CCCATGACAA CGTGAAGGTG	900
TGTGAGGAGG TGTTTGGGAA GCTCAGAGCC AACCACATGA TGTCTCCGAC ACTCATCCAG	960
ATCGACCGTG CCAACCCCTG GTCAGCCTGC AGTGCTGCCA TTATCACCGA CTTCTGGAC	1020
AGCGGCGACG GTGACTGCCT CCTGGACCAG CCCAGCAAGC CCATCACCCCT GCCTGAGGAC	1080
CTGCCAGGCA CAAGCTACAG TTTGAGCCAA CAGTGCGAGC TGGCCTTTGG GGTGGGCTCT	1140
AAGCCCTGCC CATATATGCA GTACTGTACA AAGCTGTGGT GCACCGGCAA GGCCAAGGGG	1200
CAGATGGTGT GCCAGACTCG CCACTTCCCC TGGGCAGATG GCACCAGCTG TGGTGAGGGC	1260
AAGTTCTGCC TCAAGGGAGC CTGCGTGGAG AGACACAACC CAAACAAGTA CCGGGTGGAC	1320
GGCCCTTGGG CCAAGTGGGA GCCTTATGGT CCCTGCTCGC GCACCTGCGG TGGGGGCGCG	1380
CAGCTGGCCC GGAGGCAAGT GCAAGCAACC CTACCCCTGC CAACGGGCGG GAAGTACTGC	1440
GAGGGAGTGA GAGTGAAATA CCGATCTTGC AACTTGGAGC CCTGCCCCAG CTCAGCCTCT	1500
GGCAAGAGCT TCCGGGAA	1518

Fig. 13

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THYRARAARAGQRLTGSSDLRRCFYSGYVNAEPDSFAAVSLCGGLRGAFGYQGAEYVISPLPNTSAPEAQRHSQGAHL
 LQRRGAPVGPSPDTSRCGVASGWNPAILRALDPYKPRRTGVGESHNRSSGRAKRFVSI PRYVETLVVADESMVKFHGA
 DLEHYLLTLLATAARLYRHPSILNPIINIVVKVLLLGDRDTGPKVTGNAALTLRNFCAWQKKLNKVSOKHPEYWDTAILF
 TRQDLCGATTCDTLGMADVGTMCDPKRSCSVIEDDGLPSAFTTAHELGHVFNMPHDNVKVEEVFGKLRANHHMSPTLIQ
 IDRANPWSACSAAIITDFLDSGHGDCLLDQPSKPIITLPEDLPGTSYSLSQCELAFGVGSKPCPYMQYCTKLWCTGKAKG
 QMVCQTRHFPWADGTSCGEGKFLKGACVERHNPKNYRVDPWAKWEPYGPCSRTCGGGAQLARRQVQATLPLPTGKGYC
 EGV RVKYRSCNLEPCSSASGKSF

Fig. 14

GATGCATCTAAGCCCTGGTCCAAATGCACCTTCAGCCACCATCACAGAATTCCTGGATGATGGCCATGGTAACTGTTTGCT
 GGACCTACCACGAAAGCAGATCCTGGGCCCCGAAGAACTCCAGGACAGACCTACGATGCCACCCAGCAGTGCAACCTTA
 CATTGGGCCCTGAGTACTCCGTGTGTCCCGGCATGGATGTCGTGTCTCCCTGTGGTGTGCTGTGGTACGCCAGGGCCAG
 ATGGTCTGTCTGACCAAGAAGCTTCCTGCGGTGGAAGGACGCCTTGTTGGAAGGGGAGAATCTGCCTGCAGGGCAAAATG
 TGTGGACAAAACCAAGAAAAAATATTATTCAACGCTAAGCCATGGCAACTGGGGATCTTGGGGATCCTGGGGCCAGTGTT
 CTCGCTCATGTGGAGGAGGAGTGCAAGTTTGCCTATCGTCGTGTAATAACCCTGCTCCCAGAAACAACGGACGCTACTGC
 ACAGGGAAGAGGGCCATCTACCGCTCCTGCAGTCTCATGCCCTGCCACCCAATGGTAAATCATTTGTCATGAACAGTG
 TGAGGCCAAAATGGCTATCAGTCTGATGCAAAAGGAGTCAAACTTTTGTGAATGGGTTCCCAATATGCAAGTGTC
 TGCCCGCGATGTGTGCAAGCTGACCTGCAGAGCCAAAGGACTGGCTACTATGTGGTATTTTCTCAAAGGTGACCGAT
 GGCCTGAATGTAGGCGTACAGTAATCCGTCTGCGTCCGGGGGAAGTGTGTGAGAACTGGCTGTGACGGCATCATTGG
 CTCAAAGCTGCAGTATGACAAGTGCGGAGTATGTGGAGGAGACAACCTCCAGCTGTACAAAGATTGTTGGAACCTTTAATA
 AGAAAAGTAAGGGTTCANCTGACGTGGTGAGGATTCCTGAAGGGGCAACCCACATAAAAGTTCGACAGTTCAAAGCCAAA
 GACCAGACTAGATTCACTGCCTATTTAGCCCTGAAAAAGAAAAACGGTGAGTACCTTATCAATGGAAGTACATGATCTC
 CACTTCAGAGACTATCATTGACATCAATGGAACAGTCATGAACATAGCGGTTGGAGCCACAGGGATGACTTCCTGCATG
 GCATGGGCTACTCTGCCACGAAGGAAATTCTAATAGTGAGATTCTTGCAACAGACCCCACTAAACCATTAGATGTCCGT
 TATAGCTTTTTTGTTCCTCAAGAGTCCACTCCAAAAGTAACTCTGTCACTAGTCATGGCAGCAATAAAGTGGGATCACA
 CACTTCGCAGCCGAGTGGGTACGGGCCCATGGCTCGCTGCTCTAGGACCTGTGACACAGGTTGGCACACCAGAACGG
 TGCAGTGCCAGGATGGAAACCGGAAGTTAGCAAAAGGATGCTCTCTCCCAAGGCCCTTCTGCGTTTAAGCAATGCTTG
 TTGAAGAAATGTTAG

Fig. 15

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DASKPWSKCTSATITEFLDDGHGNCLLDLPRKQILGPEELPGQTYDATQQCNLTFGPEYSVCPGMDVCAPLWCAVVRQGO
MVCLTKKLPAVEGTPCGKGRIQLQKCVDKTKKKYYSTSSHGNWGSWGSWGQCSRSCGGGVQFAYRRCNNPAPRNNGRYC
TGKRAIYRSCSLMPCPPNGKSRHEQCEAKNGYQSDAKGVKTFVEWVPKYASVLPDVCKLTCRAKGTGYVVFSPKVTD
GTECRPYSNSVCVRGKCVRTGCDGIIGSKLQYDKCGVCGGDNSSCTKIVGTFNKKSXGSDVVRIPGATHIKVRQFKAK
DQTRFTAYLALKKNGEYLINGKYMISTSETIIDINGTMNYSGWSHRDDFLHGMGYSATKEILIVQILATDPTKPLDVR
YSFFVPKKSTPKVNSVTSHGSNKVGSHTSQPQWVTGPWLACSRCTDGTGWHTRTVQCQDGNRKLAKGCPLSQRPFAFKQCL
LKKC

Fig. 16

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M - - - - -		Majority			
		10	20	30	40
1	M - - - - - G D V Q - R A A R S - - - - - R G S L S A H M L	mADAMTS-1			
1	- - - - -	hADAMTS-2			
1	- - G I R - - - - -	hADAMTS-3			
1	L L G A R Q Y R R N S G P P T P A P E T S I A N S K H P A R L S R A A P P G A Q	rADAMTS-4			
1	M - - - - - S Q T G S H P G R G L A G R - - - W L W G A Q P C L L L	KIAA0688			
1	S L - - - - -	KIAA0366			
1	M D G R W Q C S - - - - -	KIAA0605			
- - - - - L L L L A L - T V L L S A D - - A G - P - - - E E E L		Majority			
		50	60	70	80
20	- - - - - L L L L A S I T M L L C A R G A H G R P T E E D E E L	mADAMTS-1			
1	- - - - -	hADAMTS-2			
4	- - - - -	hADAMTS-3			
41	R T M R L E W A S L L L L L L L C A S C L A L A A D N P A A A P A Q D K T R Q	rADAMTS-4			
27	P I V P L S W - - - L V W L L L L L L A S L L P S A R - - L A S P L P R E E E I	KIAA0688			
3	- - - - - W L I A A A L V E V R T S A D G Q A G N E E M V Q I D L	KIAA0366			
9	- - - - - C W A W F L L V L A V V A G D T V S T G S T O N S P T S N S L E G G T	KIAA0605			
V - - - - P - - - - - L R G - - - P - G - - G T T S R L -		Majority			
		90	100	110	120
47	V L - - - P S - - - - - L E R A - - - P - G H D S T T T R L -	mADAMTS-1			
1	- - - - -	hADAMTS-2			
4	- - - - -	hADAMTS-3			
91	P R - - - A A A A A Q P D Q R Q W E E T Q E R G H L Q P L A R Q R R S S G L V	rADAMTS-4			
62	V F - - - P E - - - - - K L N G S V L P - G - S G T P A R L L	KIAA0688			
31	P I K R Y R E Y E L V T P V S T N L E G R Y L S H T L S A S H K K R S A R D V S	KIAA0366			
44	D A T A F W - - - - - W G E W T K W T A F S R S C G G G V T S Q E R	KIAA0605			
- N L D - - - - - G - - - - L - L E R D S G V - A P G - -		Majority			
		130	140	150	160
65	- R L D A F - - - - - G Q Q L H L K L Q P D S G F L A P G F T	mADAMTS-1			
1	- - - - -	hADAMTS-2			
4	- - - - - G R V D - - - - -	hADAMTS-3			
118	Q N I D Q L Y S G G G K V G Y L V Y A G G R R F L L D L E R D D T V G A A G G I	rADAMTS-4			
83	C R L Q A F - - - - - G E T L L L E L E Q D S G V Q V E G L T	KIAA0688			
71	S N P E Q L F - - - - - F N I T A F G K D F H L R L K P N T Q L V A P G A V	KIAA0366			
73	H C L Q - - - - - Q R R K S V P G P G - -	KIAA0605			

Fig. 17A

[illegible]

Fig. 17B

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	-----GLAHT--S-----RRTKRFASEARF-	Majority
	330 340 350 360	
214	---PVRDPTPOGAGKPSGPGS-----IRKKRFVSSPRY-	mADAMTS-1
1	-----RTKRFBVSEARF-	hADAMTS-2
108	ALNSGLATEAFSAYGNKTONTREKRTTHRRRTKRFLSYPRF-	hADAMTS-3
279	----LLDHSASFSPAGNAGPQTW----WRRRRRSISRARQ-	rADAMTS-4
209	-----RAKRFBASLSRF-	KIAA0688
232	NIHQQLNET-----MRRRRRHAGENDYN	KIAA0366
219	KYRKGNALHGYSLVTHIPAGARDIQIVERKK-----S	KIAA0605
	VEVLLVADDSMAAFHGAG-LQNYLLTLMSIAARIYKHPSI	Majority
	370 380 390 400	
244	VETMLVADQSMADFHGSG-LKHVELLTLFSVAARFYKHPSI	mADAMTS-1
12	VETLLVADASMAAFYGAD-LQNFLLTLMSVAARIYKHPSI	hADAMTS-2
147	VEVLVADNRMVSYHGEN-LQHYLLTLMSID-----	hADAMTS-3
310	VELLLVADSSMAKMYGRG-LQHYLLTLASIANRLYSHASI	rADAMTS-4
220	VETLVVADDKMAAFHGAG-LKRYLLTVMAAAAKAFKHPSI	KIAA0688
254	IEVLLGVDDSVVRFHGKEHVQNYLLTLMNIIVNEIYHDESL	KIAA0366
251	ADVLALADEAGYFFNG----NYKVD----SPKNFNIAGT	KIAA0605
	RNSISLVVVKVVVLGDEKKGPEVSX-NAALTLRNFCNWQH	Majority
	410 420 430 440	
283	RNSISLVVVKILVIYEEQKGPEVTS-NAALTLRNFCNWQK	mADAMTS-1
51	KNSINLMVVKVLIVEDEKKGPEVSD-NGGLTLRNFCNWQR	hADAMTS-2
177	-----GPSISF-NAQTTLKNLCQWQH	hADAMTS-3
349	ENHIRLAVVKVVVLT--KSEVSK-NAATTLKNFCKWQH	rADAMTS-4
259	RNPVSLVVTSLVILGSGEGPQVGP-SAAQTLSRSCAWQR	KIAA0688
294	GVHINVVLVRMIMLGYAKSISLIERGNPSRSLENVCRWAS	KIAA0366
283	VVKYR----RPHDVYETGIEYIVAQGPTNQGLNVM-VWNQ	KIAA0605
	QHNSPSDRHPEHYDTAILLTRQDLCGSHG-CDTLGMADV G	Majority
	450 460 470 480	
322	QHNSPSDRDPEHYDTAILLTRQDLCGSHT-CDTLGMADV G	mADAMTS-1
90	RFNQPSDRHPEHYDTAILLTRQNFCCGQEGLCDTLGVADIG	hADAMTS-2
197	SKNSPGGI--HHDTAVLLTRQDICRAHDKCDTLGLAELG	hADAMTS-3
386	QHNLGDDHEEHYDAAILLFTREDLCGHHS-CDTLGMADV G	rADAMTS-4
298	GLNTPEDSDPDHFDTAILLTRQDLCGVST-CDTLGMADV G	KIAA0688
334	QQQRSDLNHSEHHDHAIFLTRODF-GPAGM--QGYAPVT	KIAA0366
318	NGKSPSIT----FEYTLLOPPHE--SRPQPIYYGFSESA	KIAA0605

Fig. 17C

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		T I C D P X R S C S V I E D D G L Q A A F T V A H E L G H V L N M P H D - D S K	Majority
		490 500 510 520	
361	mADAMTS-1	T V C D P S R S C S V I E D D G L Q A A F T T A H E L G H V F N M P H D - D A K	
130	hADAMTS-2	T I C D P N K S C S V I E D E G L Q A A H T L A H E L G H V L S M P H D - D S K	
234	hADAMTS-3	T I C D P Y R S C S I S E D S G L S T A F T T A H E L G H V F N M P H D - D N N	
425	rADAMTS-4	T E C S P E R S C A V I E D D G L H A A F T V A H E I G H L L G L S H D - D S K	
337	KIAA0688	T V C D P A R S C A I V E D D G L Q S A F T A A H E L G H V F N M L H D - N S K	
370	KIAA0366	G M C H P V R S C T L N H E D G F S S A F V V A H E T G H V L G M E H D G Q G N	
351	KIAA0605	-----E S Q G L D G A -----G L M G F I P H N G ---	
		P C - S L N G P X G S S R H V M - A P L L X H L D H S X P W S P C S A Q E I T E	Majority
		530 540 550 560	
400	mADAMTS-1	H C A S L N G V T G D S - H L M - A S M L S S L D H S Q P W S P C S A Y M V T S	
169	hADAMTS-2	P C T R L F G P H G K H - H V M - A P L F V H L N Q T L P W S P C S A M Y L T E	
273	hADAMTS-3	K C K E - - E G V K S P Q H V M - A P T L N F Y T N P W M W S K C S R K Y I T E	
464	rADAMTS-4	F C E E N F G S - T E D K R L M - S S I L T S I D A S K P W S K C T S A T I T E	
376	KIAA0688	P C I S L N G P L S T S R H V M - A P V M A H V D P E E P W S P C S A R F I T D	
410	KIAA0366	R C - - - G D E T A M G S V M - A P L V Q A A F H R Y H W S R C S G Q E L K R	
369	KIAA0605	- - - S L Y G Q A S S E R L G L D N R L F G H P G L D M E L G P S Q G Q E T N E	
		F - L D N G H G D C L L D K P E A - P L P L P V E L P G - - I L Y D A D E Q C C O	Majority
		570 580 590 600	
438	mADAMTS-1	F - L D N G H G E C L M D K P Q N - P I K L P S D L P G - - T L Y D A N R Q C Q	
207	hADAMTS-2	L - L D G G H G D C L L D A P A A - A L P L P T G L P G R M A L Y Q L D Q Q C R	
310	hADAMTS-3	F - L D T G Y G E C L L N E P E S R P Y P L P V Q L P G - - I L Y N V N K Q C E	
502	rADAMTS-4	F - L D D G H G H C L L D V P R K - Q I L G P E E L P G Q T - - Y D A T Q Q C N	
415	KIAA0688	F - L D N G Y G H C L L D K P E A - P L H L P V T F P G K D - - Y D A D R Q C Q	
445	KIAA0366	Y - I H S Y - - D C L L D D P F O H D W P K L P E L P G - - I N Y S M D E Q C R	
406	KIAA0605	V C E Q A G G G A C - E G P P R G K G F R D R N V T G T P L T G D K D D E E V D	
		L T F G P G S K H C P X F S A - D V C A Q L W C A G V D - G G H X V C Q T K H G	Majority
		610 620 630 640	
474	mADAMTS-1	F T F G E E S K H C P D A A S - - T C T T L W C T G T S - G G L L V C Q T K H -	
245	hADAMTS-2	Q I F G P D F R H C P N T S A Q D V C A Q L W C H - T D - G A E P L C H T K N G	
347	hADAMTS-3	L I F G P G S Q V C P Y H M Q - - C R R L W C N N V N - G V H K G C R T Q H T	
538	rADAMTS-4	L T F G P E Y S V C P G H - - D V C A R L W A A V V R - Q G Q H V C L T K K -	
451	KIAA0688	L T F G P D S R H C P Q L P P P - - C A A L W C S G H L - N G H A M C Q T K H S	
480	KIAA0366	F D F G V G Y K M C T A F R T F D P C K Q L W C S H P D - N P Y - F C K T K K G	
445	KIAA0605	T H F A S Q - - - E F F S A N A I S D Q L L G A G S D L K D F T L N E T V N S	

Fig. 17D

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	- - P W A D G T P C G P G K A - C K A G S - C V P K E E N E R - - P V V D G G W	Majority
	650 660 670 680	
510	- F P W A D G T S C G E G K W - C V S G K - C V N K T D M K H F A T P V H G S W	mADAMTS-1
283	S L P W A D G T P C G P G H L - C S E G S - C L P E E E V E R P K P V V D G G W	hADAMTS-2
383	- - P W A D G T E C E P G K H - C K Y G - F C V P K - E M C - - V P Y T D G S W	hADAMTS-3
573	- L P A V R A L P V G K E E S A C K A N V W T K L R K N I T R H Q A M E I G G P	rADAMTS-4
488	- - P W A D G T P C G P A Q A - C M G G R - C L H M D Q L Q D F N I P Q A G G W	KIAA0688
518	- - P P L D G T E C A A G K W - C Y K G H - C M W K N A N Q Q - - - K Q D G N W	KIAA0366
481	I F A - - Q G A P - - - - - R S S L A E S F F V D Y E E N E - - - - -	KIAA0605
	G P W G P W G D C S R T C G G S V Q F S L R E C N N P V P K N G G K Y C E G R -	Majority
	690 700 710 720	
547	G P W G P W G D C S R T C G G G V Q Y T M R E C D N P V P K N G G K Y C E G K -	mADAMTS-1
321	A P W G P W G E C S R T C G G G V Q F S H R E C K D P E P Q N G G R Y C L G R -	hADAMTS-2
416	G S W S P F G T C S R T C G G G I K T A I R E C N R P E P K N G G K Y C V G R -	hADAMTS-3
612	G A P G V - - - - S V L A L A G E E Y S L P T A I A I T P H L E T V A A T A Q G	rADAMTS-4
524	G P W G P W G D C S R T C G G G V Q F S S R D C T R P V P R N G G K Y C E G R -	KIAA0688
551	G S W T K F G S C S R T C G T G V R F R T R Q C N N P M P I N G G Q D C P G - V	KIAA0366
504	- - - - - G A G P Y L L N G S Y - - L E L S S D R V A N S S S	KIAA0605
	R A K Y Q S C N T E D C P K H X G K T F R A E Q C A K Y N - A F S Y X N K G X X	Majority
	730 740 750 760	
586	R V R Y R S C N I E D C P D N N G K T F R E E Q C E A H N - E F S K A S F G N E	mADAMTS-1
360	R A K Y Q S C H T E E C P P D - G K S F R E E Q C E K Y N - A Y N Y T D M D G N	hADAMTS-2
455	R M K F K S C N T E P C L K O K - R D F R D E Q C A H F D G K H F N I N - G L L	hADAMTS-3
648	R G P Y - T V P A V S Y P A H L T A N L S A T S S V K P K M A I S P M O K E S K	rADAMTS-4
563	R T R F R S C N T E D C P T G S A L T F R E E Q C A A Y N - H R T D L F K S F P	KIAA0688
590	N F E Y Q L C N T E E C Q K H F E - D F R A Q Q C Q Q R N S H F E Y Q N T K H -	KIAA0366
528	E A P F P N V S T S L L T S A G N R T H K A R T R P K A R K Q - - - - G V S P A	KIAA0605
	P X V E W V P K Y A G V S P K D R C K L T C R A K G T G Y Y Y V L E P K V V D G	Majority
	770 780 790 800	
625	P T V E W T P K Y A G V S P K D R C K L T C E A K G I G Y F F V L Q P K V V D G	mADAMTS-1
398	- L L Q W V P K Y A G V S P R D R C K L F C R A R G R S E F K V F E A K V I D G	hADAMTS-2
493	P N V R W V P K Y S G I L M K D R C K L F C R V A G N T A Y Y Q L R D R V I D G	hADAMTS-3
687	T F V E W V P K Y A G V L P A D V C K L T C R A K G T G Y Y V V F S P K V T D G	rADAMTS-4
602	G P M D W V P R Y T G V A P O D Q C K L T C Q A R A L G Y Y Y V L E P R V V D G	KIAA0688
628	- - - H W L P - Y E H P D P K K R C H L Y C S K E T G D V A Y M K Q L V H D G	KIAA0366
564	D M Y R W K - - - - - L S S H E P C S A T C T T G V N S A Y - - - - -	KIAA0605

Fig. 17E

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TPCS - PDSNSVCVRGQCVKAGCDEIGSKKKFDKCGVCGG		Majority
	810 820 830 840	
665	TPCS - PDSTSVCVQGGQCVKAGCDRIIDSKKKFDKCGVCGG	mADAMTS-1
437	TLCG - PETLAICVRGQCVKAGCDHVVDSEFWKLDKCGVCGG	hADAMTS-2
533	TPCG - QDTNDICVGG - CROAGCDHVLNSKARRDKCGVCGG	hADAMTS-3
727	TECR - PYSNSVCVRGRCVRTGCDGIIGSKLQYDKCGVCGG	rADAMTS-4
642	TPCS - PDSSSVCVQGRCIHAGCDRIIGSKKKFDKCMVCGG	KIAA0688
664	THCSYKDPYSICVRGECVKVGCDKEIGSNKVEDKCGVCGG	KIAA0366
589	-----AMCVR-----	KIAA0605
DGSSCKKVSGTFTKT - - RYGYNDVVTIPAGATN:LVQRQS		Majority
	850 860 870 880	
704	NGSTCKKMSGIVTST - - RPGYHDIVTIPAGATNIEVKHRN	mADAMTS-1
476	KGKSCRKSGSGLTP - - VYGYNDIVTIPAGATNIDVKQRS	hADAMTS-2
572	DNSSCKTVAGTFNTV - - IYGYNTVVRIPAGATNIDVRQHS	hADAMTS-3
766	DNSSCTKIIGTFNKK - - SKGYTDVVRIPAGATHIKYRQFK	rADAMTS-4
681	DGSGCSKQSGSFRKF - - RYGYNNVVTIPAGATHILVRQQG	KIAA0688
704	DNSHCRTVKGTFTTRTPRKLGYLKMFDIPPGARHVLIQEDE	KIAA0366
594	-----YDGV-----	KIAA0605
ASGHTN - - NYLALKX - ADGEYLLNGNFTLSTSETDIDLKG		Majority
	890 900 910 920	
742	QRGSRNNGSFLAIRA - ADGTYILNGNFTLSTLEGDLTYKG	mADAMTS-1
514	HPGVQNDGNYLALKT - ADGQYLLNGNLAISAEQDILVKG	hADAMTS-2
610	FSGETDDDNYLALSS - SKGEFLNGNFVVTMAKREIRIGN	hADAMTS-3
804	AKDQTRFTAYLALKK - KTGEYLLNGKYMISTSETIDING	rADAMTS-4
719	NPGHRS - - IYLALKL - PDGSYALNGEYTLMPSPDVLPG	KIAA0688
744	ASPH - - - - ILAIKNQATGHYILNGKGEEAKSRTFIDL - -	KIAA0366
598	-----	KIAA0605
TV - LRYSGSSAALERLHS - - - PLKEPLTVQVLAV - GXT -		Majority
	930 940 950 960	
781	TV - LRYSGSSAALERIRS - - FSPLKEPLTIQVLM7 - GHAL	mADAMTS-1
553	TI - LKYSGSIATLERLQS - - FRPLPEPLTVQLLAVPGEVF	hADAMTS-2
649	AV - VEYSGSETAVERINSTD - - RIEQELLQVLSV - GKLY	hADAMTS-3
843	TV - MNYSGWSHRDDFLHGMGYSATKEILIVQILA - TDPTK	rADAMTS-4
756	AVSLRYSGATAASETLSG - - HGPLAOPPLTLQVL - VAGNPQ	KIAA0688
777	GVEWDYN - IEDDIESLHTDG - - PLHDPVIVLIIPQENDT -	KIAA0366
598	EVDDSYCOALTRPEPVHE - - - - -	KIAA0605

Fig. 17F

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R P D V R Y S F F V P - - - - -		Majority
	970 980 990 1000	
817 R P K I K F T Y F M - - - - -	mADAMTS-1	
590 P P K V K Y T F F V P N D - - - - -	hADAMTS-2	
685 N P D V R Y S F N I P T E D K P - - - - - Q Q F Y W N S H G P W Q	rADAMTS-3	
831 A L D V R H S F F V P - - - - -	rADAMTS-4	
793 D T R L R Y S F F V P - - - - -	KIAA0688	
813 R S S L T Y K Y I I H E D S V P T I N S N N V I Q E E L D T F E W - A L K S W S	KIAA0366	
616 - - - - - F C A G R E C Q P R - - - - - W E T - S S W S	KIAA0605	
- - - - -		Majority
	1010 1020 1030 1040	
827 - - - - -	mADAMTS-1	
593 - - - - -	hADAMTS-2	
713 A C S K P C Q G E R K - R K L V C T R E S D - - - Q L T V S D Q R C D R L P Q P	hADAMTS-3	
892 - - - - -	rADAMTS-4	
804 - - - - -	KIAA0688	
852 Q V S K P C G G G F Q Y T K Y G C R R K S D - - - N K M V H R S F C E A N K K P	KIAA0366	
633 E C S R T C G E G Y Q F R V V R C W K M L S P G F D S S V Y S D L C E A A E A V	KIAA0605	
- - - - -		Majority
	1050 1060 1070 1080	
827 - - - - -	mADAMTS-1	
603 - - - - - V - D F S - - -	hADAMTS-2	
749 G H I - T E P C G T - D C D L R - W H V A S R S E C S A Q C G L - G Y R T L D I	hADAMTS-3	
892 - - - - -	rADAMTS-4	
804 - - - - -	KIAA0688	
889 K P I - R R M C N I Q E C T H P L W V A E E W E H C T K T C G S S G Y Q L R T V	KIAA0366	
673 R P E E R K T C R N P A C G - P Q W E M S E N S E C T A K C G E R S V V T R D I	KIAA0605	
- - - - - K V T - - - S S N T R P T - R X X - - - - -		Majority
	1090 1100 1110 1120	
827 - - - - - K K K T E - - - S F N A I P T F - S E - - - - -	mADAMTS-1	
607 - - - - - M Q S S K E R A T - - - T N I T Q P L L H A Q - - - - -	hADAMTS-2	
785 Y C A K Y S R L D G K T E K V D D G F C S S H P K P S N R E K C S G E C N T G G	hADAMTS-3	
892 - - - - -	rADAMTS-4	
804 - - - - - R P T - - - P S T P R P T - P Q D - - - - -	KIAA0688	
928 R C L Q - P L L D G T N R S V H S K Y C M G D - R P E S R R P C N R V P C P A Q	KIAA0366	
712 R C S E - - - - - D E K L C D P N T R P V G E K N C T G P P C D R Q	KIAA0605	

Fig. 17G

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		W V - G D W G E C S K T C G - G T Q R R X V - C R D - D G - V - - - S E C - K A				Majority
		1130	1140	1150	1160	
842	W V I E E W G E C S K T C G S G W Q R R V V Q C R D I N G H P - - A S E C A K E					mADAMTS-1
627	W V L G D W S E C S S T C G A G W Q R R T V E C R D P S G Q A - - S A T C N K A					hADAMTS-2
825	W R Y S A W T E C S K S C D G G T Q R R R A I C V N T R N D V L D D S K C T H Q					hADAMTS-3
892	- - - - -					rADAMTS-4
817	W L - - - - - H R R A - - - - - Q !					KIAA0688
966	W K T G P W S E C S V T C G E G T E V R Q V L C R A G D H C D G E K P E S V R A					KIAA0366
741	W T V S D W G P C S G S C G Q G R T I R H V Y C K T S D G R V V P E S Q C O H -					KIAA0605
		- - L K P L X X R P C - - - K S - - C P - - W - - - D W S - - - - - C - -				Majority
		1170	1180	1190	1200	
880	- - V K P A S T R P C - - - A D L P C P - H W Q V G D W S P - - - - - C S K					mADAMTS-1
665	- - L K P E D A K P C - - - E S - - - - -					hADAMTS-2
865	- - E K V T I Q R - C - - S E F P C P - Q W K S G D W S E - - - - - C L V					hADAMTS-3
892	- - - - -					rADAMTS-4
825	- - L E I L R R R P - - - - - W A - - - - -					KIAA0688
1006	C Q L P P C N D E P C L G D K S I F C Q - M E V L A R Y C S I P G Y N K L C C E					KIAA0366
780	- E T K P L A I H P C - G D K N - - C P A H W L A Q D W E R - - - - - C N T					KIAA0605
		T C G K - - - - - K K P T -				Majority
		1210	1220	1230	1240	
907	T C G K - - - - - G Y K K R T L					mADAMTS-1
676	- - - - -					hADAMTS-2
891	T C G K - - - - - G H K H R Q V					hADAMTS-3
892	- - - - - K K P A X					rADAMTS-4
835	- - G R - - - - -					KIAA0688
1045	S C S K R S S T L P P P Y L L E A A E T H D D V I S N P S D L P R S L V M P T S					KIAA0366
809	T C G R G V K K R L V L C M E L A N G K P Q T R S G P E C G L A K - - K P P E E					KIAA0605
		K V - - - - - S A - - - - - D T				Majority
		1250	1260	1270	1280	
918	K C V - - - - - S A - - - - - D G					mADAMTS-1
676	- - - - -					hADAMTS-2
902	W C Q F G E D R L N D R M C D P E V D A A A N S A - - - - - D T					hADAMTS-3
897	K V N - - - - - S A - - - - - D T					rADAMTS-4
837	- - - - -					KIAA0688
1085	L V P Y H S E T P A K K M S L S S I S S V G G P N A Y A A F R P N S K - - P D G					KIAA0366
847	S T C F - - E R P C F K W Y T S P W S E C T K T C G V G V R M R D V K C Y Q G T					KIAA0605

Fig. 17H

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	D G L - Q E S P - - P - - - - - P - - K P - - - - Q L C P L S Q C	Majority
	1290 1300 1310 1320	
925	G V L S N E S C - - D - - - - - P L K K P K H Y I D F C T L T Q C	mADAMTS-1
676	- Q L C P L	hADAMTS-2
929	D G L Q E S S P - - P - - - - - I P I W K P S I F S H V - P S S R I	hADAMTS-3
904	D G L - Q E S S - - P - - - - - P	rADAMTS-4
837	- -	KIAA0688
1123	A N L R Q R S A - - Q Q A G S K T V R L V T V P S S P P T K R V H L S S A S Q M	KIAA0366
885	D I V R G C D P L V K P V G R Q A C D L Q P C P T E P P D D S C Q D Q P G T N C	KIAA0605
	A -	Majority
	1330 1340 1350 1360	
951	S	mADAMTS-1
681		hADAMTS-2
955	P	hADAMTS-3
912		rADAMTS-4
837	K	KIAA0688
1161	A A A S F F A A S D S I G A S S Q A R T S K K D G K I I D N R R P T R S S T L E	KIAA0366
925	A L A I - - - - - K V N L C G H W Y Y S K A C C R - - - S C R P P H S	KIAA0605
-		Majority
-		
951		mADAMTS-1
681		hADAMTS-2
955		hADAMTS-3
912		rADAMTS-4
837		KIAA0688
1201	R	KIAA0366
951		KIAA0605

Fig. 17I

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Bovine ADAMTS 4 DNA

```
TTTAGGGAGG AGCAGTGTGA GGCCAAAAAT GGATATCAGT CTGATGCAAA AGGAGTCAAA 60
ACGTTTGTGG AATGGGTTC CAAATATGCT GGTGTCCTGC CCGGAGACGT GTGCAAACTG 120
ACCTGCAGAG CTAAGGGCAC TGGCTACTAC GTGGTGTCT CTCCAAAGGT GACCGATGGG 180
ACAGAGTGCA GGCCATACAG CAATTCCGTG TGTGTCCGGG GGAAGTGTGT GCGGACAGGC 240
TGTGACAGCA TCATTGGCTC GAAGCTGCAG TATGACAAAT GTGGCGTCTG TGGAGGAGAC 300
AACTCCAGTT GCACAAAGGT GGTCCGAACC TTCAATAAAA AAAGTAAGGG TTACTGAC 360
GTCGTGAGGA TCCCCGAAGG GCGGACTCAC ATAAAAGTCC GACAGTTCAA AGCCAAAGAC 420
CAG 423
```

Fig. 18

Bovine ADAMTS 4 Protein

```
FREEQCEAKNGYQSDAKGVKTFVWPKYAGVLPQDVCKLTCRAKGTGYVVVFSKVTGTECRPYSNSVCVRGKCVRTG
CDSIIIGSKLQYDKCGVCGGDNSSCTKVVGTFNKKSKGYTDVVRIPGATHIKVRQFKAKDQ
```

Fig. 19

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Bovine 0688 DNA

GGAAACCTG GCCATTGGA GCAACTACCT GGCCTGAAG CTCCCCGATG GTCCTATGC	60
CCTCAACGGT GAATACACGC TGATCCCGTC CCCCACAGAC GTGGTACTGC CCGGGGCCGT	120
CAGCCTGGCG TACAGCGGG CCACTGCAGC CTGGGAGACA CTGTCAGGAC ACGGGCCCCT	180
GGCTGAGCCC TTAACGCTGC AGGTCCTAGT GCTGGCAAC CCGCAGAAC CCCGCCTCAG	240
ATACAGCTTT TTCGTGCCG GACCGCGACC GGTCCCTCC ACGCCACGCC CCACTCCCA	300
GGACTGGCTG CGCCGCAAGT CACAGATTCT GGAGATCTC CGCGGCGCT CCTGGGCGG	360
CAGGAAATAA CCTCACCATC CCGCTGCCC TTTCTGGCA CCGGGCCTC GGACTTAGCT	420
GGGTGAACGA GAGACCTCTG CAGCGGCTC ACCCGAGAC ATCGTGGGG AGGGGCTTAG	480
TGAGCCCGC CTCTCTCCC CGCGTACCG AGCAGGCTGG CCTGCCGGG GTTTCCTGCC	540
CTGGATGGCT GGTGGATGA AGGGGCTGG AGATTGTCC CTATCTAAC TGCCCCCTCT	600
GCCCTGCTGG TCACAGGAGG GAGGGGAAG GCAGGGA	637

Fig. 20

Bovine KIAA 0688 Protein

ETLAWSNYLALKLPDGSYALNGEYTLIPSPDVLPGAVSLRYSGATAASETLSGHGPLAEPLTQVLVAGNPQNARLR
 YSFFVPRPRVPSTPRPTQDLRRKSQILEILRRRSWAGRK

Fig. 21

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Human ADAMTS 5 DNA

```

ACTCACTATA GGGCTCGTGC GGCCGCCCGG GCAGGTATCT TTAAGCATCC CAGCATCCTC   60
AACCCCATCA ACATCGTTGT GGTCAAGGTG CTGCTTCTTA GAGATCGTGA CTCGGGGCCC   120
AAGGTCACCG GCAATGCGGC CCGACGCTG CGCAACTTCT GTGCCTGGCA GAAGAAGCTG   180
AACAAAGTGA GTGACAAGCA CCCCAGGTAC TGGGACACTG CCATCCTCTT CACCAGGCAG   240
GACCTGTGTG GAGCCACCAC CTGTGACACC CTGGGCATGG CTGATGTGGG TACCATGTGT   300
GACCCCAAGA GAAGCTGCTC TGTATTGAG GACGATGGGC TTCCATCAGC CTTCACTACT   360
GCCACGAGC TGGGCCACGT GTTCAACATG CCCCATGACA ATGTGAAAGT CTGTGAGGAG   420
GTGTTTGGGA AGCTCCGAGC CAACCACATG ATGTCCCGA CCCTCATCCA GATCGACCGT   480
GCCAACCCCT GGTGAGCTG CAGTGTCTGC ATCATCACC ACTTTCTGGA CAGCGGGCAC   540
GGTGACTGCC TCCTGGACCA ACCCAGCAAG CCCATCTTCC TGGCGAGNGA TCTGCCGGGC   600
GCCAGCTACA CCCTGAGCCA GCARTGCGAG CTGGCTTTTG GCGTGGGCTT CAAGCCCTGT   660
CCTTACATGC AGTACTGCAC CAAGCTGTGG TGCACCGGA AGGCCAAGGG ACAGATGGTG   720
TGCCAAACCC GCCACTTCCC CTGGGCCGAT GGCACCAATT GTGGCGAGGG CAAGTTCTGC   780
CTCAAAGGGG CCTGCGTGA AARACACAAC CTCAACAAGC ACAGGGTGA TGGTTCCTGG   840
GCCAAATGGG ATCCCTATGG CCCCTGCTCG CGCACATGTG GTGGGGCGT GCAGCTGGCC   900
AGGAGGCAGN TGCACCAACC CCANCCCTG CCAACNGGG GCAAGTACTG CGAGGGAGTG   960
AGGGTGAAT ACCGATCCTG CAACCTGGAG CCTGCCCCA GCTCAGCCTC CGGAAAGAGC  1020
TTCCGGGAGG AGCAGTGTGA GGCTTTCAAC GGCTACAACC ACAGCACCAA CCGGCTCACT  1080
CTCGCCGTGG CATGGGTGCC CAAGTACTCC GCGTGTCTC CCCGTGACAA GTGTAAGCTC  1140
ATC                                     1143

```

Fig. 22

Human ADAMTS 5 Protein

```

THYRARAARAGIFKHPSILNPINIVVVKVLLLRDRDSGPKVTGNAALTLRNFCAWQKLNKVS DKHP EYWDAILFTRQ
DLGATTCDLGMADVGTMCOPKRSCSVIEDDGLPSAFTTAHELGHVFNMPHDNVKVC EEVFGKLRANHMMSP TL IQIDR
ANPWSACSAAIITDFLDSGHGDCLLDQPSKPIFLPXDLP GASYTLSQQCELA FGVGFKPCPYMQYCTKLWCTGKAKGMV
CQTRHFPWADGTSCGEGKFLKGACVEXHNLNKH RV DGSWAKWDPYGPCSRTCGGGVQLARRQXHQXP LPTGGKYCEGV
RVKYRSCNLEPCSSASGKSFREEQCEAFNGYNHSTNRLTLAVAWPKYSGVSPROKCKLI

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Fig. 23

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Rat ADAMTS 2 DNA

TCCGCCCTTC	CGGGAGGAAC	AGTGTGAAAA	ATATAATGCC	TACAACCACA	CGGACCTGGA	60
TGGGAATTTC	CTTCAGTGGG	TCCCCAAATA	CTCAGGAGTG	TCCCCCGAG	ACCGATGCAA	120
ACTGTTTTC	AGAGCCCGTG	GGAGGAGTGA	GTTCAAAGTG	TTTGAAACTA	AGGTGATCGA	180
TGGCACTCTG	TGCGGACCGG	ATACTCTGGC	CATCTGTGTG	CGGGGACAGT	GCGTTAAGGC	240
TGGCTGTGAC	CATGTGGTGA	ACTCACCTAA	GAAGCTGGAC	AAGTGGCGTA	TCTGTGG	297

Fig. 24

Rat ADAMTS 2 Protein

PPFREEQCEKYNAYNHTDLDGNFLQWVPKYSGVSPDRCKLFCRARGRSEFKVFETKVIDGTLCPDTLAICVRGQCVKA
GCDHVVNSPKLDKCGIC

Fig. 25

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Rat ADAMTS 3 DNA

CCCCTGGATG TGGTCAAAGT GCAGTCGGAA GTACATCACC GAGTTCTTAG ACACTGGGTA	60
TGGAGAGTGC TTGTTAAATG AACCTCAATC CAGGACCTAT CCTTTGCCCT CCCAACTGCC	120
CGGCCTTCTC TACAACGTGA ATAAACAATG TGAAGTATT TTTGGACCAG GCTCTCAAGT	180
GTGCCCATAT ATGATGCAGT GCAGACGGCT CTGGTGCAAT AACGTGGATG GAGCACACAA	240
AGGCTGCAGG ACTCAGCACA CGCCCTGGGC AGATGGAACC GAGTGTGAGC CTGGAAAGCA	300
CTGCAAGTTT GGATTCTGTG TTCCCAAAGA AATGGAGGGC CCTGCAATTG ATGGATCCTG	360
GGGAAGTTGG AGTCACTTTG GGGCCTGCTC AAGAACATGT GGAGGAGGCA TCAGAACAGC	420
CATCAGAGAG TGCAACAGAC CAGAGCCAAA AAATGGTGGG AGGTACTGTG TAGGAGGAG	480
AATRAAGTTC AAATCCTGCA ACACCGAGCC CTGCCCGAAG CACAAGCGAG ACTTCCGTGA	540
GGAGCAGTGT GCTTACTTTG ACGGCAAGCA TTTCAACATC AATGGTCTGC TGCCAGTGT	600
ACGCTGGGTC CCTAAGTACA GTGGAATTTT GATGAAGGAC CGATGCAAGT TGTTCCTCAG	660
AGTGGCAGGA AACACAGCCT ACTACCAGCT TCGAGACAGA GTGATTGACG GAACCCCTG	720
TGGCCAGGAC ACAAATGACA TCTGTGTCCA AGGCCTTTGC CGGCAAGCTG GATGTGATCA	780
TACTTTAAAC TCAAAGGCC GAAAGATAA ATGTGGGATT TGT	823

Fig. 26

Rat ADAMTS 3 Protein

PMWSKCSRKYITEFLDTGYGELLNEPQSRTYPLPSQLPGLLYNVNKQCELIFGPGSQVCPYMMQCRRLWCNNVDGAHK
 GCRTQHTPWADGTECEPGKHCKFGFCVPKEMEGPATDGSWGSWSHFGACSRTCGGGIRTAIRECNRPEPKNGGRYCVGRR
 XKFKSCNTEPCPKHKRDFREEQCAYFDGKHFNINGLLPSVRWVPKYSGLMKDRCKLFCRVAGNTAYYQLRDRVIDGTPC
 GQDTNDICVQGLCRQAGCDHTLNSKARKDKCGIC

Fig. 27

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brevican + TS-4

brevican

Fig. 28

MQFVSWATLL TLLVRDLAEMGSPDAAAIVRKORLHPRQVKLLETIGEYEVSPIRWALGEPPPTNVHFKRTRRSINSAT
 DPWPAFASSSSSTSSQAHYRLSAFGQQFLFNL TANAGFTAPLFTVTLTGTPGVNQTIFYSEEEAEELKHCFYKGYVNTNS
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 ARKNGERINLAGDVAALNSGLATEAFSAVGNTDNTREKRTKRFLSYPRFVEVLVWADNRMVSYHGENLQHYILTL
 cysteine switch *
 potential furin cleavage sites metallopeptidase domain
 MSIVASIKDPSIGNL INIVIVNLIVIHNEQDGPSISFNAQTLLKNLCQWQHSKNSPGGIHHDITAVLL TRQDICRAHDKC
 Zn binding Met turn
 DTLGLAELGTICDPYRSCSISEDGSLSTAFTHAELGHVFNPHDDNNKCKEKGKSPQHVNAPTILNFYTNPMWWSKCSR
 disintegrin-like domain
 KYITFELDTGYGECLLNEPESRPYPLPVQLPGILYNVWKQCELIFGPGSQVCPYMQCRLLWCNNVNGVHKGCRTQHTPW
 TSP 1 motif
 ADGTECEPGKHCKYGFVCPKEMDVPVTDGSMGSMSPFGTCSRTCGGGIKTAIRECNRPEPKNGGKYCVGRRMKFKSCNTE
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 PCLKQKRDRDEQCAHFDGKHFNINGLLPNVRWVPKYSGILLMKORCKLFCRVAGNTAYYQLRDRVIDGTPCGQDITNDICV
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 TSP1-like submotif 1 TSP1-like submotif 2
 WNSHGPHQACSKPCQGERKRLVCTRESQQLTVSDQRCDRLPOPQGHITPCGTDGCDLRHWHVSRSECSAQCGGLGYRTLDI
 TSP1-like submotif 3
 YCAKYSRLDGKTEKVDDGFCSSHPKPSNREKCSGECNTGGWRYSAWTECSKSCGGGTQRRRAICVNTNRNDVLDOSKCTHQ
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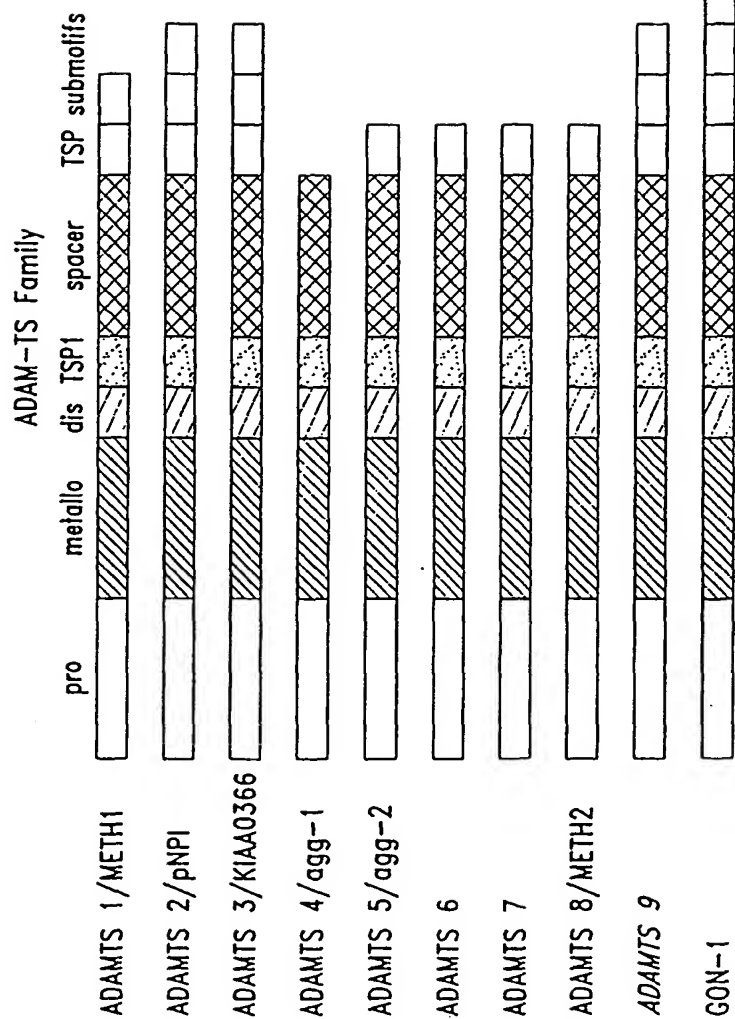


Fig. 30A

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CONSENSUS	HEXXHXXGXXHD
Fertilin α	HELGHNLGIRHD
ADAM 17/TACE	HELGHNFGAEHD
ADAM 10/Kuz	HEIGHNFCSPHD
ADAMTS 1	HELGHVFNMPHD
ADAMTS 2	HETGHVLGMEHD
ADAMTS 4	HELGHVFNMLHD
ADAMTS 5	HEIGHLLGLSHD
ADAMTS 9	HELGHVFNMPHD
GON-1	HELGHVFSIPHD

Fig. 30B

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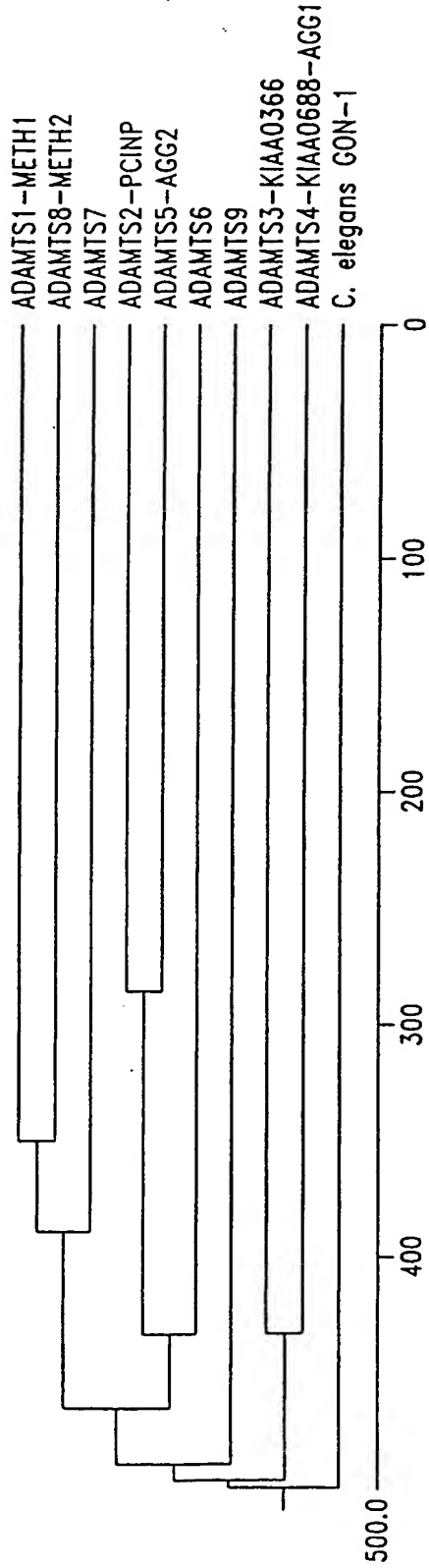


Fig. 30C

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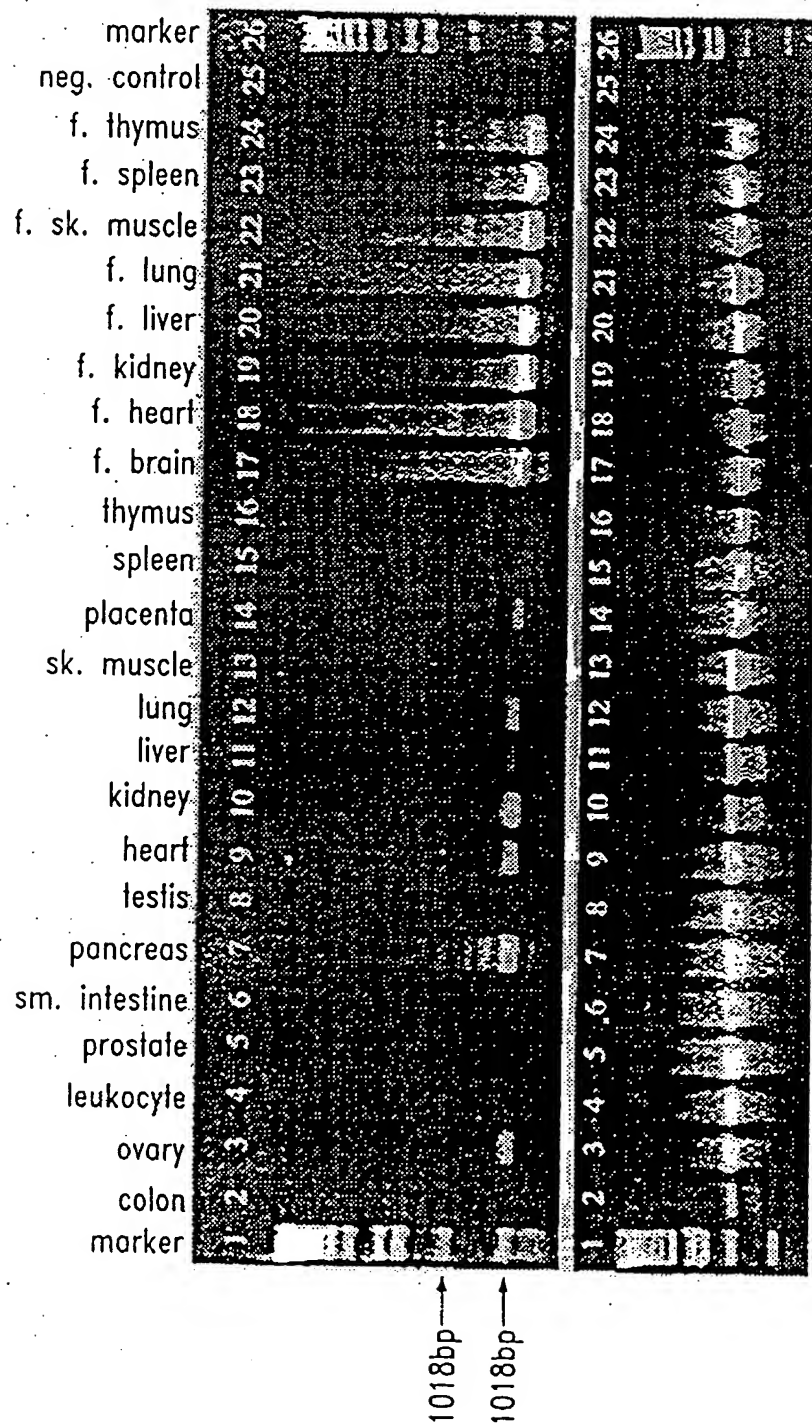


Fig. 31

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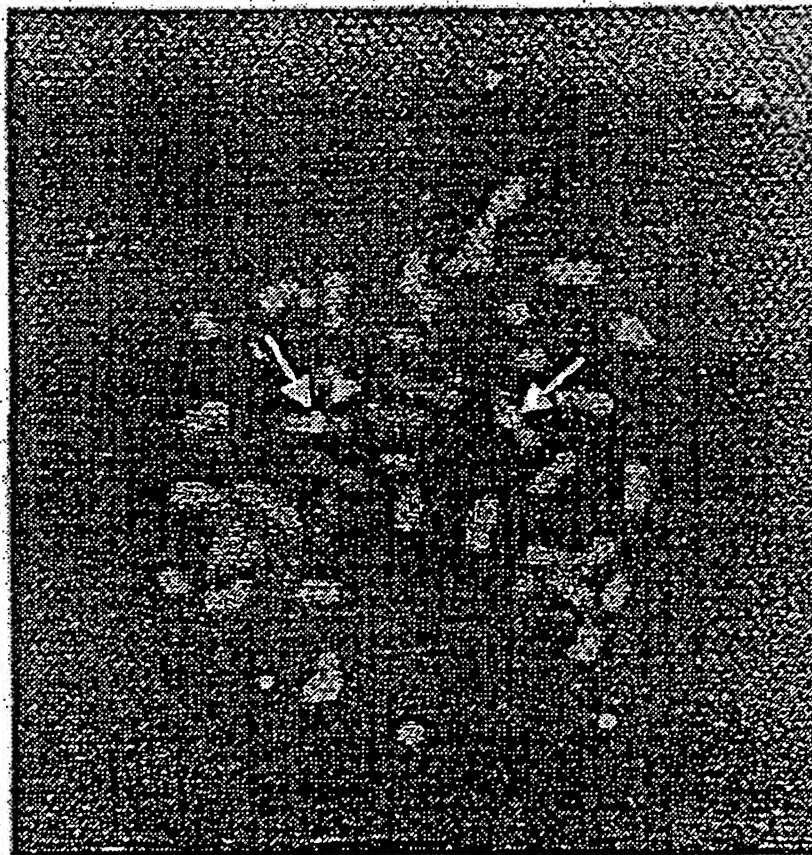


Fig. 32A

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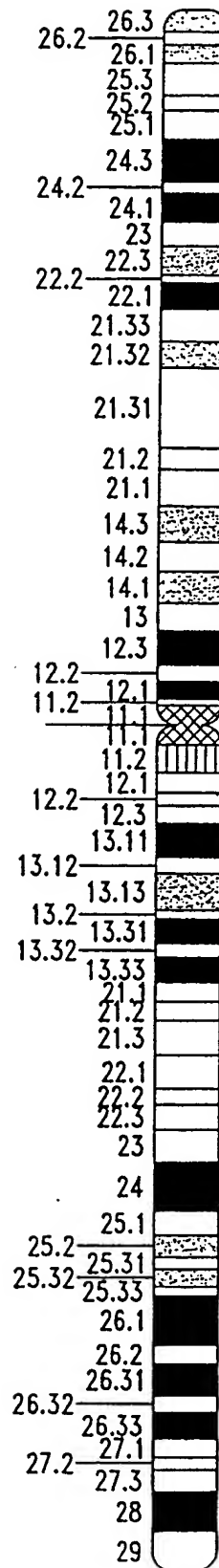
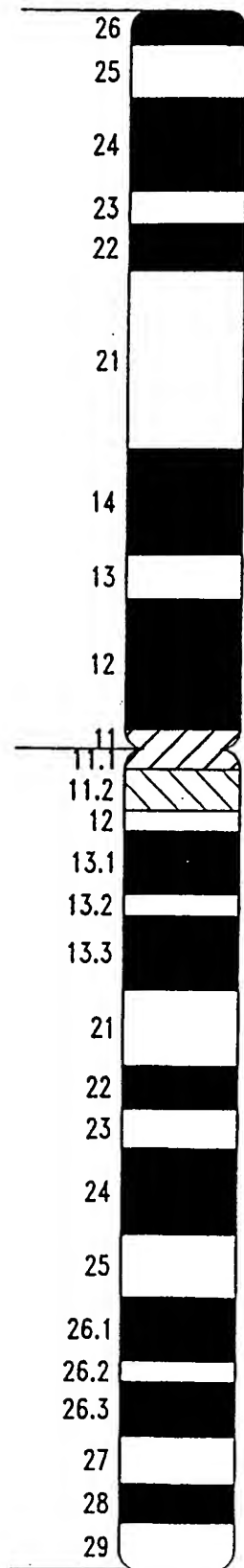


Fig. 32B

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<110> Neurocrine Biosciences, Inc.
 Kelner, Gregory S.
 Clark, Melody
 Maki, Richard A.

<120> METALLOPROTEINASES AND METHODS OF USE
 THEREFOR

<130> 690068.453PC

<140> PCT

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35     40     45
Ser Ile Lys Asn Ser Ile Asn Leu Met Val Val Lys Val Leu Ile Val
50     55     60
Glu Asp Glu Lys Trp Gly Pro Glu Val Ser Asp Asn Gly Gly Leu Thr
65     70     75     80
Leu Arg Asn Phe Cys Asn Trp Gln Arg Arg Phe Asn Gln Pro Ser Asp
85     90     95
Arg His Pro Glu His Tyr Asp Thr Ala Ile Leu Leu Thr Arg Gln Asn
100    105    110
Phe Cys Gly Gln Glu Gly Leu Cys Asp Thr Leu Gly Val Ala Asp Ile
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130    135    140
Gly Leu Gln Ala Ala His Thr Leu Ala His Glu Leu Gly His Val Leu
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Ser Met Pro His Asp Asp Ser Lys Pro Cys Thr Arg Leu Phe Gly Pro
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Thr Leu Pro Trp Ser Pro Cys Ser Ala Met Tyr Leu Thr Glu Leu Leu
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Gln Gln Cys Arg Gln Ile Phe Gly Pro Asp Phe Arg His Cys Pro Asn
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 Glu Glu Cys Pro Pro Asp Gly Lys Ser Phe Arg Glu Gln Gln Cys Glu
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 Lys Tyr Asn Ala Tyr Asn Tyr Thr Asp Met Asp Gly Asn Leu Leu Gln
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 Trp Lys Leu Asp Lys Cys Gly Val Cys Gly Gly Lys Gly Asn Ser Cys
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 485 490 495
 Ile Val Thr Ile Pro Ala Gly Ala Thr Asn Ile Asp Val Lys Gln Arg
 500 505 510
 Ser His Pro Gly Val Gln Asn Asp Gly Asn Tyr Leu Ala Leu Lys Thr
 515 520 525
 Ala Asp Gly Gln Tyr Leu Leu Asn Gly Asn Leu Ala Ile Ser Ala Ile
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 Glu Gln Asp Ile Leu Val Lys Gly Thr Ile Leu Lys Tyr Ser Gly Ser
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<211> 870

<212> PRT

<213> Rattus norvegicus

<220>

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<223> Xaa = Any Amino Acid

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<211> 951

<212> PRT

<213> Homo sapien

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65          70          75          80
Ser Val Pro Gly Pro Gly Asn Arg Thr Cys Thr Gly Thr Ser Lys Arg
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Tyr Gln Leu Cys Arg Val Gln Glu Cys Pro Pro Asp Gly Arg Ser Phe
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Arg Glu Glu Gln Cys Val Ser Phe Asn Ser His Val Tyr Asn Gly Arg
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<211> 5774

<212> DNA

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<210> 8

<211> 1201

<212> PRT

<213> Homo sapien

<400> 8

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Lys Arg Tyr Arg Glu Tyr Glu Leu Val Thr Pro Val Ser Thr Asn Leu
35          40          45
Glu Gly Arg Tyr Leu Ser His Thr Leu Ser Ala Ser His Lys Lys Arg
50          55          60
Ser Ala Arg Asp Val Ser Ser Asn Pro Glu Gln Leu Phe Phe Asn Ile
65          70          75          80
Thr Ala Phe Gly Lys Asp Phe His Leu Arg Leu Lys Pro Asn Thr Gln
85          90          95

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Leu Val Ala Pro Gly Ala Val Val Glu Trp His Glu Thr Ser Leu Val
 100 105 110
 Pro Gly Asn Ile Thr Asp Pro Ile Asn Asn His Gln Pro Gly Ser Ala
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 Thr Tyr Arg Ile Arg Lys Thr Glu Pro Leu Gln Thr Asn Cys Ala Tyr
 130 135 140
 Val Gly Asp Ile Val Asp Ile Pro Gly Thr Ser Val Ala Ile Ser Asn
 145 150 155 160
 Cys Asp Gly Leu Ala Gly Met Ile Lys Ser Asp Asn Glu Glu Tyr Phe
 165 170 175
 Ile Glu Pro Leu Glu Arg Gly Lys Gln Met Glu Glu Glu Lys Gly Arg
 180 185 190
 Ile His Val Val Tyr Lys Arg Ser Ala Val Glu Gln Ala Pro Ile Asp
 195 200 205
 Met Ser Lys Asp Phe His Tyr Arg Glu Ser Asp Leu Glu Gly Leu Asp
 210 215 220
 Asp Leu Gly Thr Val Tyr Gly Asn Ile His Gln Gln Leu Asn Glu Thr
 225 230 235 240
 Met Arg Arg Arg Arg His Ala Gly Glu Asn Asp Tyr Asn Ile Glu Val
 245 250 255
 Leu Leu Gly Val Asp Asp Ser Val Val Arg Phe His Gly Lys Glu His
 260 265 270
 Val Gln Asn Tyr Leu Leu Thr Leu Met Asn Ile Val Asn Glu Ile Tyr
 275 280 285
 His Asp Glu Ser Leu Gly Val His Ile Asn Val Val Leu Val Arg Met
 290 295 300
 Ile Met Leu Gly Tyr Ala Lys Ser Ile Ser Leu Ile Glu Arg Gly Asn
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 Pro Ser Arg Ser Leu Glu Asn Val Cys Arg Trp Ala Ser Gln Gln Gln
 325 330 335
 Arg Ser Asp Leu Asn His Ser Glu His His Asp His Ala Ile Phe Leu
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 Thr Arg Gln Asp Phe Gly Pro Ala Gly Met Gln Gly Tyr Ala Pro Val
 355 360 365
 Thr Gly Met Cys His Pro Val Arg Ser Cys Thr Leu Asn His Glu Asp
 370 375 380
 Gly Phe Ser Ser Ala Phe Val Val Ala His Glu Thr Gly His Val Leu
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 405 410 415
 Met Gly Ser Val Met Ala Pro Leu Val Gln Ala Ala Phe His Arg Tyr
 420 425 430
 His Trp Ser Arg Cys Ser Gly Gln Glu Leu Lys Arg Tyr Ile His Ser
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 450 455 460
 Pro Glu Leu Pro Gly Ile Asn Tyr Ser Met Asp Glu Gln Cys Arg Phe
 465 470 475 480
 Asp Phe Gly Val Gly Tyr Lys Met Cys Thr Ala Phe Arg Thr Phe Asp
 485 490 495
 Pro Cys Lys Gln Leu Trp Cys Ser His Pro Asp Asn Pro Tyr Phe Cys
 500 505 510
 Lys Thr Lys Lys Gly Pro Pro Leu Asp Gly Thr Glu Cys Ala Ala Gly
 515 520 525
 Lys Trp Cys Tyr Lys Gly His Cys Met Trp Lys Asn Ala Asn Gln Gln

530		535		540
Lys Gln Asp Gly Asn Trp Gly Ser Trp Thr Lys Phe Gly Ser Cys Ser				
545		550		555
Arg Thr Cys Gly Thr Gly Val Arg Phe Arg Thr Arg Gln Cys Asn Asn				560
	565		570	575
Pro Met Pro Ile Asn Gly Gly Gln Asp Cys Pro Gly Val Asn Phe Glu				
	580		585	590
Tyr Gln Leu Cys Asn Thr Glu Glu Cys Gln Lys His Phe Glu Asp Phe				
	595	600		605
Arg Ala Gln Gln Cys Gln Gln Arg Asn Ser His Phe Glu Tyr Gln Asn				
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Thr Lys His His Trp Leu Pro Tyr Glu His Pro Asp Pro Lys Lys Arg				
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Cys His Leu Tyr Cys Gln Ser Lys Glu Thr Gly Asp Val Ala Tyr Met				640
	645		650	655
Lys Gln Leu Val His Asp Gly Thr His Cys Ser Tyr Lys Asp Pro Tyr				
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Ser Ile Cys Val Arg Gly Glu Cys Val Lys Val Gly Cys Asp Lys Glu				
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Ile Gly Ser Asn Lys Val Glu Asp Lys Cys Gly Val Cys Gly Gly Asp				
690		695		700
Asn Ser His Cys Arg Thr Val Lys Gly Thr Phe Thr Arg Thr Pro Arg				
705		710		715
Lys Leu Gly Tyr Leu Lys Met Phe Asp Ile Pro Pro Gly Ala Arg His				
	725		730	735
Val Leu Ile Gln Glu Asp Glu Ala Ser Pro His Ile Leu Ala Ile Lys				
	740		745	750
Asn Gln Ala Thr Gly His Tyr Ile Leu Asn Gly Lys Gly Glu Glu Ala				
	755	760		765
Lys Ser Arg Thr Phe Ile Asp Leu Gly Val Glu Trp Asp Tyr Asn Ile				
770		775		780
Glu Asp Asp Ile Glu Ser Leu His Thr Asp Gly Pro Leu His Asp Pro				
785		790		795
Val Ile Val Leu Ile Ile Pro Gln Glu Asn Asp Thr Arg Ser Ser Leu				
	805		810	815
Thr Tyr Lys Tyr Ile Ile His Glu Asp Ser Val Pro Thr Ile Asn Ser				
	820		825	830
Asn Asn Val Ile Gln Glu Glu Leu Asp Thr Phe Glu Trp Ala Leu Lys				
	835		840	845
Ser Trp Ser Gln Val Ser Lys Pro Cys Gly Gly Gly Phe Gln Tyr Thr				
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Lys Tyr Gly Cys Arg Arg Lys Ser Asp Asn Lys Met Val His Arg Ser				
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Phe Cys Glu Ala Asn Lys Lys Pro Lys Pro Ile Arg Arg Met Cys Asn				
	885		890	895
Ile Gln Glu Cys Thr His Pro Leu Trp Val Ala Glu Glu Trp Glu His				
	900		905	910
Cys Thr Lys Thr Cys Gly Ser Ser Gly Tyr Gln Leu Arg Thr Val Arg				
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Cys Leu Gln Pro Leu Leu Asp Gly Thr Asn Arg Ser Val His Ser Lys				
	930		935	940
Tyr Cys Met Gly Asp Arg Pro Glu Ser Arg Arg Pro Cys Asn Arg Val				
945		950		955
Pro Cys Pro Ala Gln Trp Lys Thr Gly Pro Trp Ser Glu Cys Ser Val				
	965		970	975

Thr Cys Gly Glu Gly Thr Glu Val Arg Gln Val Leu Cys Arg Ala Gly
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 Asp His Cys Asp Gly Glu Lys Pro Glu Ser Val Arg Ala Cys Gln Leu
 995 1000 1005
 Pro Pro Cys Asn Asp Glu Pro Cys Leu Gly Asp Lys Ser Ile Phe Cys
 1010 1015 1020
 Gln Met Glu Val Leu Ala Arg Tyr Cys Ser Ile Pro Gly Tyr Asn Lys
 1025 1030 1035 1040
 Leu Cys Cys Glu Ser Cys Ser Lys Arg Ser Ser Thr Leu Pro Pro
 1045 1050 1055
 Tyr Leu Leu Glu Ala Ala Glu Thr His Asp Asp Val Ile Ser Asn Pro
 1060 1065 1070
 Ser Asp Leu Pro Arg Ser Leu Val Met Pro Thr Ser Leu Val Pro Tyr
 1075 1080 1085
 His Ser Glu Thr Pro Ala Lys Lys Met Ser Leu Ser Ser Ile Ser Ser
 1090 1095 1100
 Val Gly Gly Pro Asn Ala Tyr Ala Ala Phe Arg Pro Asn Ser Lys Pro
 1105 1110 1115 1120
 Asp Gly Ala Asn Leu Arg Gln Arg Ser Ala Gln Gln Ala Gly Ser Lys
 1125 1130 1135
 Thr Val Arg Leu Val Thr Val Pro Ser Ser Pro Pro Thr Lys Arg Val
 1140 1145 1150
 His Leu Ser Ser Ala Ser Gln Met Ala Ala Ala Ser Phe Phe Ala Ala
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<210> 9

<211> 2868

<212> DNA

<213> Homo sapien

<400> 9

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<210> 10

<211> 958

<212> PRT

<213> Homo sapien

<400> 10

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 35           40           45
Glu Glu Glu Gln Asn Lys Pro His Ile Ile Tyr Arg Arg Ser Ala Pro
 50           55           60
Gln Arg Glu Pro Ser Thr Gly Arg His Ala Cys Asp Thr Ser Glu His
 65           70           75           80
Lys Asn Arg His Ser Lys Asp Lys Lys Lys Thr Arg Ala Arg Lys Trp
 85           90           95
Gly Glu Arg Ile Asn Leu Ala Gly Asp Val Ala Ala Leu Asn Ser Gly
 100          105          110
Leu Ala Thr Glu Ala Phe Ser Ala Tyr Gly Asn Lys Thr Asp Asn Thr
 115          120          125
Arg Glu Lys Arg Thr His Arg Arg Thr Lys Arg Phe Leu Ser Tyr Pro
 130          135          140

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 His Gly Glu Asn Leu Gln His Tyr Ile Leu Thr Leu Met Ser Ile Asp
 165 170 175
 Gly Pro Ser Ile Ser Phe Asn Ala Gln Thr Thr Leu Lys Asn Leu Cys
 180 185 190
 Gln Trp Gln His Ser Lys Asn Ser Pro Gly Gly Ile His His Asp Thr
 195 200 205
 Ala Val Leu Leu Thr Arg Gln Asp Ile Cys Arg Ala His Asp Lys Cys
 210 215 220
 Asp Thr Leu Gly Leu Ala Glu Leu Gly Thr Ile Cys Asp Pro Tyr Arg
 225 230 235 240
 Ser Cys Ser Ile Ser Glu Asp Ser Gly Leu Ser Thr Ala Phe Thr Ile
 245 250 255
 Ala His Glu Leu Gly His Val Phe Asn Met Pro His Asp Asp Asn Asn
 260 265 270
 Lys Cys Lys Glu Glu Gly Val Lys Ser Pro Gln His Val Met Ala Pro
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 Thr Leu Asn Phe Tyr Thr Asn Pro Trp Met Trp Ser Lys Cys Ser Arg
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 Lys Tyr Ile Thr Glu Phe Leu Asp Thr Gly Tyr Gly Glu Cys Leu Leu
 305 310 315 320
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 325 330 335
 Ile Leu Tyr Asn Val Asn Lys Gln Cys Glu Leu Ile Phe Gly Pro Gly
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 355 360 365
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 370 375 380
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 Lys Thr Ala Ile Arg Glu Cys Asn Arg Pro Glu Pro Lys Asn Gly Gly
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 Pro Cys Leu Lys Gln Lys Arg Asp Phe Arg Asp Glu Gln Cys Ala His
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 530 535 540
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 545 550 555 560
 Ala Arg Arg Asp Lys Cys Gly Val Cys Gly Asp Asn Ser Ser Cys
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 Lys Thr Val Ala Gly Thr Phe Asn Thr Val His Tyr Gly Tyr Asn Thr

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Ser Lys Gly Glu Phe Leu Leu Asn Gly Asn Phe Val Val Thr Met Ala
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      675      680      685
Arg Tyr Ser Phe Asn Ile Pro Ile Glu Asp Lys Pro Gln Gln Phe Tyr
      690      695      700
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      725      730      735
Val Ser Asp Gln Arg Cys Asp Arg Leu Pro Gln Pro Gly His Ile Thr
      740      745      750
Glu Pro Cys Gly Thr Asp Cys Asp Leu Arg Trp His Val Ala Ser Arg
      755      760      765
Ser Glu Cys Ser Ala Gln Cys Gly Leu Gly Tyr Arg Thr Leu Asp Ile
      770      775      780
Tyr Cys Ala Lys Tyr Ser Arg Leu Asp Gly Lys Thr Glu Lys Val Asp
      785      790      795      800
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      805      810      815
Ser Gly Glu Cys Asn Thr Gly Gly Trp Arg Tyr Ser Ala Trp Thr Glu
      820      825      830
Cys Ser Lys Ser Cys Asp Gly Gly Thr Gln Arg Arg Arg Ala Ile Cys
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Lys Ser Gly Asp Trp Ser Glu Cys Leu Val Thr Cys Gly Lys Gly His
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Arg Met Cys Asp Pro Glu Val Asp Ala Ala Ala Asn Ser Ala Asp Thr
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<210> 11

<211> 4303

<212> DNA

<213> Homo sapien

<400> 11

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<210> 12

<211> 840

<212> PRT

<213> Homo sapien

<400> 12

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Trp Leu Val Trp Leu Leu Leu Leu Leu Ala Ser Leu Leu Pro Ser
35      40      45
Ala Arg Leu Ala Ser Pro Leu Pro Arg Glu Glu Glu Ile Val Phe Pro
50      55      60
Glu Lys Leu Asn Gly Ser Val Leu Pro Gly Ser Gly Thr Pro Ala Arg
65      70      75      80
Leu Leu Cys Arg Leu Gln Ala Phe Gly Glu Thr Leu Leu Leu Glu Leu
85      90      95
Glu Gln Asp Ser Gly Val Gln Val Glu Gly Leu Thr Val Gln Tyr Leu
100     105     110
Gly Gln Ala Pro Glu Leu Leu Gly Gly Ala Glu Pro Gly Thr Tyr Leu
115     120     125
Thr Gly Thr Ile Asn Gly Asp Pro Glu Ser Val Ala Ser Leu His Trp
130     135     140
Asp Gly Gly Ala Leu Leu Gly Val Leu Gln Tyr Arg Gly Ala Glu Leu
145     150     155     160
His Leu Gln Pro Leu Glu Gly Gly Thr Pro Asn Ser Ala Gly Gly Pro
165     170     175
Gly Ala His Ile Leu Arg Arg Lys Ser Pro Ala Ser Gly Gln Gly Pro
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Met Cys Asn Val Lys Ala Pro Leu Gly Ser Pro Ser Pro Arg Pro Arg
195     200     205
Arg Ala Lys Arg Phe Ala Ser Leu Ser Arg Phe Val Glu Thr Leu Val
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225     230     235     240
Tyr Leu Leu Thr Val Met Ala Ala Ala Ala Lys Ala Phe Lys His Pro
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 Gly Ser Gly Glu Glu Gly Pro Gln Val Gly Pro Ser Ala Ala Gln Thr
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 Ser Asp Pro Asp His Phe Asp Thr Ala Ile Leu Phe Thr Arg Gln Asp
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 Leu Cys Gly Val Ser Thr Cys Asp Thr Leu Gly Met Ala Asp Val Gly
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 Thr Val Cys Asp Pro Ala Arg Ser Cys Ala Ile Val Glu Asp Asp Gly
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 Leu Gln Ser Ala Phe Thr Ala Ala His Glu Leu Gly His Val Phe Asn
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 Met Leu His Asp Asn Ser Lys Pro Cys Ile Ser Leu Asn Gly Pro Leu
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 Ser Thr Ser Arg His Val Met Ala Pro Val Met Ala His Val Asp Pro
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 His Leu Pro Val Thr Phe Pro Gly Lys Asp Tyr Asp Ala Asp Arg Gln
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 Pro Pro Cys Ala Ala Leu Trp Cys Ser Gly His Leu Asn Gly His Ala
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 Met Cys Gln Thr Lys His Ser Pro Trp Ala Asp Gly Thr Pro Cys Gly
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 Pro Ala Gln Ala Cys Met Gly Gly Arg Cys Leu His Met Asp Gln Leu
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 Trp Gly Asp Cys Ser Arg Thr Cys Gly Gly Gly Val Gln Phe Ser Ser
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 595 600 605
 Arg Tyr Thr Gly Val Ala Pro Gln Asp Gln Cys Lys Leu Thr Cys Gln
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 Ala Arg Ala Leu Gly Tyr Tyr Tyr Val Leu Glu Pro Arg Val Val Asp
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 Gly Thr Pro Cys Ser Pro Asp Ser Ser Ser Val Cys Val Gln Gly Arg
 645 650 655
 Cys Ile His Ala Gly Cys Asp Arg Ile Ile Gly Ser Lys Lys Phe
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 Asp Lys Cys Met Val Cys Gly Gly Asp Gly Ser Gly Cys Ser Lys Gln
 675 680 685
 Ser Gly Ser Phe Arg Lys Phe Arg Tyr Gly Tyr Asn Asn Val Val Thr

690	695	700
Ile Pro Ala Gly Ala Thr His Ile Leu Val Arg Gln Gln Gly Asn Pro		
705	710	715
Gly His Arg Ser Ile Tyr Leu Ala Leu Lys Leu Pro Asp Gly Ser Tyr		720
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Ala Leu Asn Gly Glu Tyr Thr Leu Met Pro Ser Pro Thr Asp Val Val		735
	740	745
Leu Pro Gly Ala Val Ser Leu Arg Tyr Ser Gly Ala Thr Ala Ala Ser		750
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Glu Thr Leu Ser Gly His Gly Pro Leu Ala Gln Pro Leu Thr Leu Gln		765
	770	775
Val Leu Val Ala Gly Asn Pro Gln Asp Thr Arg Leu Arg Tyr Ser Phe		780
785	790	795
Phe Val Pro Arg Pro Thr Pro Ser Thr Pro Arg Pro Thr Pro Gln Asp		800
	805	810
Trp Leu His Arg Arg Ala Gln Ile Leu Glu Ile Leu Arg Arg Arg Pro		815
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Trp Ala Gly Arg Lys Phe Ile Gly		830
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<210> 13

<211> 1518

<212> DNA

<213> Rattus norvegicus

<400> 13

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<211> 505
 <212> PRT
 <213> Rattus norvegicus

<400> 14

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Ala	Glu	Pro	Asp	Ser	Phe	Ala	Ala	Val	Ser	Leu	Cys	Gly	Gly	Leu	Arg
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Arg	Cys	Gly	Val	Ala	Ser	Gly	Trp	Asn	Pro	Ala	Ile	Leu	Arg	Ala	Leu
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His	Val	Phe	Asn	Met	Pro	His	Asp	Asn	Val	Lys	Val	Cys	Glu	Glu	Val
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Phe	Gly	Lys	Leu	Arg	Ala	Asn	His	Met	Met	Ser	Pro	Thr	Leu	Ile	Gln
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<210> 16
<211> 484

<212> PRT
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 <220>
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<400> 16

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Gln	Ile	Leu	Gly	Pro	Glu	Glu	Leu	Pro	Gly	Gln	Thr	Tyr	Asp	Ala	Thr
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Tyr	Arg	Arg	Cys	Asn	Asn	Pro	Ala	Pro	Arg	Asn	Asn	Gly	Arg	Tyr	Cys
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Cys	Val	Arg	Thr	Gly	Cys	Asp	Gly	Ile	Ile	Gly	Ser	Lys	Leu	Gln	Tyr
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Glu	Tyr	Leu	Ile	Asn	Gly	Lys	Tyr	Met	Ile	Ser	Thr	Ser	Glu	Thr	Ile
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Ile	Asp	Ile	Asn	Gly	Thr	Val	Met	Asn	Tyr	Ser	Gly	Trp	Ser	His	Arg
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Asp Asp Phe Leu His Gly Met Gly Tyr Ser Ala Thr Lys Glu Ile Leu
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 Ile Val Gln Ile Leu Ala Thr Asp Pro Thr Lys Pro Leu Asp Val Arg
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 Leu Lys Lys Cys

<210> 17
 <211> 423
 <212> DNA
 <213> Bos taurus

<400> 17
 tttagggagg agcagtgtga ggccaaaaat ggatatcagt ctgatgcaaa aggagtcaaa 60
 acgtttgtgg aatgggttcc caaatatgct ggtgtcctgc ccggagacgt gtgcaaactg 120
 acctgcagag ctaagggcac tggctactac gtggtgttct ctccaaagggt gaccgatggg 180
 acagagtgca ggccatacag caattccgtg tgtgtccggg ggaagtgtgt gcggacaggc 240
 tgtgacagca tcattggctc gaagctgcag tatgacaaat gtggcgtctg tggaggagac 300
 aactccagtt gcacaaagggt ggtcgggaacc ttcaataaaa aaagtaagggt ttacactgac 360
 gtcgtgagga tccccgaagg ggcgactcac ataaaagtcc gacagttcaa agccaaagac 420
 cag 423

<210> 18
 <211> 141
 <212> PRT
 <213> Bos taurus

<400> 18
 Phe Arg Glu Glu Gln Cys Glu Ala Lys Asn Gly Tyr Gln Ser Asp Ala
 1 5 10 15
 Lys Gly Val Lys Thr Phe Val Glu Trp Val Pro Lys Tyr Ala Gly Val
 20 25 30
 Leu Pro Gly Asp Val Cys Lys Leu Thr Cys Arg Ala Lys Gly Thr Gly
 35 40 45
 Tyr Tyr Val Val Phe Ser Pro Lys Val Thr Asp Gly Thr Glu Cys Arg
 50 55 60
 Pro Tyr Ser Asn Ser Val Cys Val Arg Gly Lys Cys Val Arg Thr Gly
 65 70 75 80
 Cys Asp Ser Ile Ile Gly Ser Lys Leu Gln Tyr Asp Lys Cys Gly Val
 85 90 95
 Cys Gly Gly Asp Asn Ser Ser Cys Thr Lys Val Val Gly Thr Phe Asn
 100 105 110
 Lys Lys Ser Lys Gly Tyr Thr Asp Val Val Arg Ile Pro Glu Gly Ala
 115 120 125
 Thr His Ile Lys Val Arg Gln Phe Lys Ala Lys Asp Gln

130

135

140

<210> 19
 <211> 637
 <212> DNA
 <213> Bos taurus

<400> 19

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ggaaaccttg gccatttga gcaactacct ggccctgaag ctccccgatg gtccttatgc      60
cctcaacggg gaatacacgc tgatcccgtc cccacagac gtggtactgc ccggggccgt      120
cagcctgccc tacagcgggg ccaactgcagc ctcgagaca ctgtcaggac acggggccct      180
ggctgagccc ttaacgctgc aggtcctagt ggctggcaac ccgcagaacg ccgcctcag      240
atacagcttt ttcgtgccgc gaccgcgacc ggtccctcc acgccacgcc ccaactccca      300
ggactggctg cgccgaagt cacagattct ggagatcctc cggcggcgct cctgggcccgg      360
caggaaataa cctcaccatc ccggctgccc tttctgggca ccggggcctc ggacttagct      420
gggtgaacga gagacctctg cagcggcctc accccgagac atcgtggggg aggggcttag      480
tgagccccgc ctctcctccc cgcgctaccg agcaggctgg ccttgccggg gtttctctgc      540
ctggatggct ggtggatgga aggggctggg agattgtccc ctatctaaac tgccccctct      600
gccctgctgg tcacaggagg gagggggaag gcaggga                                637
  
```

<210> 20
 <211> 122
 <212> PRT
 <213> Bos taurus

<400> 20

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Glu Thr Leu Ala Ile Trp Ser Asn Tyr Leu Ala Leu Lys Leu Pro Asp
 1           5           10           15
Gly Ser Tyr Ala Leu Asn Gly Glu Tyr Thr Leu Ile Pro Ser Pro Thr
           20           25           30
Asp Val Val Leu Pro Gly Ala Val Ser Leu Arg Tyr Ser Gly Ala Thr
           35           40           45
Ala Ala Ser Glu Thr Leu Ser Gly His Gly Pro Leu Ala Glu Pro Leu
           50           55           60
Thr Leu Gln Val Leu Val Ala Gly Asn Pro Gln Asn Ala Arg Leu Arg
65           70           75           80
Tyr Ser Phe Phe Val Pro Arg Pro Arg Pro Val Pro Ser Thr Pro Arg
           85           90           95
Pro Thr Pro Gln Asp Trp Leu Arg Arg Lys Ser Gln Ile Leu Glu Ile
           100          105          110
Leu Arg Arg Arg Ser Trp Ala Gly Arg Lys
           115          120
  
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<210> 21
 <211> 1143
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(1143)
 <223> n = A,T,C or G

<400> 21

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actcactata gggctcgtgc ggccgcccgg gcaggatatc ttaagcatcc cagcatcctc      60
  
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```

aaccatca acatcggtgt ggtcaagggtg ctgcttctta gagatcgtga ctccggggccc 120
aaggtcaccg gcaatgcggc cctgacgctg cgcaacttct gtgcctggca gaagaagctg 180
aacaaagtga gtgacaagca ccccgagtac tgggacactg ccatactctt caccaggcag 240
gacctgtgtg gagccaccac ctgtgacacc ctgggcatgg ctgatgtggg taccatgtgt 300
gaccccaaga gaagctgctc tgtcattgag gacgatgggc ttccatcagc cttcaccact 360
gccccagagc tggggcacgt gttcaacatg ccccatgaca atgtgaaagt ctgtgaggag 420
gtgtttggga agctccgagc caaccacatg atgtccccga cctcatcca gatcgaccgt 480
gccaaaccct ggtcagcctg cagtgtgtgc atcatcacg actttctgga cagcgggcac 540
ggtgactgcc tcctggacca acccagcaag cccatcttcc tgccgagnga tctgccgggc 600
gccagctaca ccctgagcca gcartgagc ctggcttttg gcgtgggctt caagccctgt 660
ccttacatgc agtactgcac caagctgtgg tgcaccggga aggccaaggg acagatggtg 720
tgccaaaccc gccacttccc ctgggcccgt ggaccagtt gtggcgaggg caagttctgc 780
ctcaaagggg cctgctgtga aaracacaac ctcaacaagc acaggggtga tggttcctgg 840
gccaaatggg atccctatgg cccctgtctg cgcacatgtg gtgggggctg gcagctggcc 900
aggaggcagn tgcaccaacc ccancctctg ccaacngggg gcaagtactg cgaggagtg 960
aggggtgaaat accgatcctg caacctggag cctgccccca gctcagctc cgaaagagc 1020
ttccgggagg agcagtgtga ggctttcaac ggctacaacc acagcaccaa ccggctcact 1080
ctcgcctgtg catgggtgcc caagtactcc ggcgtgtctc cccgtgacaa gtgtaagctc 1140
atc 1143

```

<210> 22

<211> 381

<212> PRT

<213> Homo sapien

<220>

<221> VARIANT

<222> (1)...(381)

<223> Xaa = Any Amino Acid

<400> 22

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Thr His Tyr Arg Ala Arg Ala Ala Arg Ala Gly Ile Phe Lys His
1 5 10 15
Pro Ser Ile Leu Asn Pro Ile Asn Ile Val Val Val Lys Val Leu Leu
20 25 30
Leu Arg Asp Arg Asp Ser Gly Pro Lys Val Thr Gly Asn Ala Ala Leu
35 40 45
Thr Leu Arg Asn Phe Cys Ala Trp Gln Lys Lys Leu Asn Lys Val Ser
50 55 60
Asp Lys His Pro Glu Tyr Trp Asp Thr Ala Ile Leu Phe Thr Arg Gln
65 70 75 80
Asp Leu Cys Gly Ala Thr Thr Cys Asp Thr Leu Gly Met Ala Asp Val
85 90 95
Gly Thr Met Cys Asp Pro Lys Arg Ser Cys Ser Val Ile Glu Asp Asp
100 105 110
Gly Leu Pro Ser Ala Phe Thr Thr Ala His Glu Leu Gly His Val Phe
115 120 125
Asn Met Pro His Asp Asn Val Lys Val Cys Glu Glu Val Phe Gly Lys
130 135 140
Leu Arg Ala Asn His Met Met Ser Pro Thr Leu Ile Gln Ile Asp Arg
145 150 155 160
Ala Asn Pro Trp Ser Ala Cys Ser Ala Ala Ile Ile Thr Asp Phe Leu
165 170 175
Asp Ser Gly His Gly Asp Cys Leu Leu Asp Gln Pro Ser Lys Pro Ile
180 185 190

```

Phe Leu Pro Xaa Asp Leu Pro Gly Ala Ser Tyr Thr Leu Ser Gln Gln
 195 200 205
 Cys Glu Leu Ala Phe Gly Val Gly Phe Lys Pro Cys Pro Tyr Met Gln
 210 215 220
 Tyr Cys Thr Lys Leu Trp Cys Thr Gly Lys Ala Lys Gly Gln Met Val
 225 230 235 240
 Cys Gln Thr Arg His Phe Pro Trp Ala Asp Gly Thr Ser Cys Gly Glu
 245 250 255
 Gly Lys Phe Cys Leu Lys Gly Ala Cys Val Glu Xaa His Asn Leu Asn
 260 265 270
 Lys His Arg Val Asp Gly Ser Trp Ala Lys Trp Asp Pro Tyr Gly Pro
 275 280 285
 Cys Ser Arg Thr Cys Gly Gly Gly Val Gln Leu Ala Arg Arg Gln Xaa
 290 295 300
 His Gln Pro Xaa Pro Leu Pro Thr Gly Gly Lys Tyr Cys Glu Gly Val
 305 310 315 320
 Arg Val Lys Tyr Arg Ser Cys Asn Leu Glu Pro Cys Pro Ser Ser Ala
 325 330 335
 Ser Gly Lys Ser Phe Arg Glu Glu Gln Cys Glu Ala Phe Asn Gly Tyr
 340 345 350
 Asn His Ser Thr Asn Arg Leu Thr Leu Ala Val Ala Trp Val Pro Lys
 355 360 365
 Tyr Ser Gly Val Ser Pro Arg Asp Lys Cys Lys Leu Ile
 370 375 380

<210> 23

<211> 297

<212> DNA

<213> Rattus norvegicus

<400> 23

tccgcccttc	cgggaggaac	agtgtgaaaa	atataatgcc	tacaaccaca	cggacctgga	60
tgggaatttc	cttcagtggg	tccccaata	ctcaggagtg	tcccccgag	accgatgcaa	120
actgttttgc	agagcccgtg	ggaggagtga	gttcaaagtg	tttgaaacta	aggtgatcga	180
tggcactctg	tgcggaccgg	atactctggc	catctgtgtg	cggggacagt	gcgttaaggc	240
tggctgtgac	catgtggtga	actcacctaa	gaagctggac	aagtgcggta	tctgtgg	297

<210> 24

<211> 98

<212> PRT

<213> Rattus norvegicus

<400> 24

Pro	Pro	Phe	Arg	Glu	Glu	Gln	Cys	Glu	Lys	Tyr	Asn	Ala	Tyr	Asn	His
1				5					10					15	
Thr	Asp	Leu	Asp	Gly	Asn	Phe	Leu	Gln	Trp	Val	Pro	Lys	Tyr	Ser	Gly
		20						25					30		
Val	Ser	Pro	Arg	Asp	Arg	Cys	Lys	Leu	Phe	Cys	Arg	Ala	Arg	Gly	Arg
		35					40					45			
Ser	Glu	Phe	Lys	Val	Phe	Glu	Thr	Lys	Val	Ile	Asp	Gly	Thr	Leu	Cys
	50					55					60				
Gly	Pro	Asp	Thr	Leu	Ala	Ile	Cys	Val	Arg	Gly	Gln	Cys	Val	Lys	Ala
65				70					75					80	
Gly	Cys	Asp	His	Val	Val	Asn	Ser	Pro	Lys	Lys	Leu	Asp	Lys	Cys	Gly
				85					90					95	

Ile Cys

<210> 25
 <211> 823
 <212> DNA
 <213> Rattus norvegicus

<400> 25
 cccctggatg tgggtcaaagt gcagtcggaa gtacatcacc gagttcttag aactgggta 60
 tggagagtgc ttgttaaagt aacctcaatc caggacctat cctttgcctt cccaactgcc 120
 cggccttctc tacaacgtga ataaacaatg tgaactgatt tttggaccag gctctcaagt 180
 gtgcccatat atgatgcagt gcagacggct ctggtgcaat aacgtggatg gagcacacaa 240
 aggtgcagg actcagcaca cgccctgggc agatggaacc gagtgtgagc ctggaaagca 300
 ctgcaagttt ggattctgtg ttcccaaaga aatggagggc cctgcaattg atggatcctg 360
 gggaagtgg agtcactttg gggcctgtc aagaacatgt ggaggaggca tcagaacagc 420
 catcagagag tgcaacagac cagagccaaa aaatgggtgg aggtactgtg tagggaggag 480
 aatraagtgc aaatcctgca acaccgagcc ctgcccgaag cacaagcgag acttccgtga 540
 ggagcagtgt gcttactttg acggcaagca tttcaacatc aatgggtctg tgcccagtgt 600
 acgtgggtc cctaagtaca gtggaatgtt gatgaaggac cgatgcaagt tgttctgcag 660
 agtggcagga aacacagcct actaccagct tcgagacaga gtgattgacg gaaccccctg 720
 tggccaggac acaaatgaca tctgtgtcca aggcctttgc cggcaagctg gatgtgatca 780
 tactttaaac tcaaaggccc ggaaagataa atgtgggatt tgt 823

<210> 26
 <211> 274
 <212> PRT
 <213> Rattus norvegicus

<220>
 <221> VARIANT
 <222> (1)...(274)
 <223> Xaa = Any Amino Acid

<400> 26
 Pro Trp Met Trp Ser Lys Cys Ser Arg Lys Tyr Ile Thr Glu Phe Leu
 1 5 10 15
 Asp Thr Gly Tyr Gly Glu Cys Leu Leu Asn Glu Pro Gln Ser Arg Thr
 20 25 30
 Tyr Pro Leu Pro Ser Gln Leu Pro Gly Leu Leu Tyr Asn Val Asn Lys
 35 40 45
 Gln Cys Glu Leu Ile Phe Gly Pro Gly Ser Gln Val Cys Pro Tyr Met
 50 55 60
 Met Gln Cys Arg Arg Leu Trp Cys Asn Asn Val Asp Gly Ala His Lys
 65 70 75 80
 Gly Cys Arg Thr Gln His Thr Pro Trp Ala Asp Gly Thr Glu Cys Glu
 85 90 95
 Pro Gly Lys His Cys Lys Phe Gly Phe Cys Val Pro Lys Glu Met Glu
 100 105 110
 Gly Pro Ala Ile Asp Gly Ser Trp Gly Ser Trp Ser His Phe Gly Ala
 115 120 125
 Cys Ser Arg Thr Cys Gly Gly Gly Ile Arg Thr Ala Ile Arg Glu Cys
 130 135 140
 Asn Arg Pro Glu Pro Lys Asn Gly Gly Arg Tyr Cys Val Gly Arg Arg
 145 150 155 160

[illegible]

<210> 27

<211> 1073

<212> PRT

<213> Homo sapien

<400> 27

Met 1	Gln	Phe	Val	Ser 5	Trp	Ala	Thr	Leu 10	Leu	Thr	Leu	Val	Arg 15	Asp
Leu	Ala	Glu	Met 20	Gly	Ser	Pro	Asp 25	Ala	Ala	Ala	Ala	Val 30	Arg 35	Asp
Arg	Leu	His 35	Pro	Arg	Gln	Val	Lys 40	Leu	Leu	Glu	Thr	Leu 45	Gly	Tyr
Glu	Ile 50	Val	Ser	Pro	Ile	Arg 55	Val	Asn	Ala	Leu	Gly 60	Glu	Pro	Phe
Thr 65	Asn	Val	His	Phe 70	Lys	Arg	Thr	Arg	Arg	Ser 75	Ile	Asn	Ser	Ala
Asp	Pro	Trp	Pro	Ala 85	Phe	Ala	Ser	Ser	Ser	Ser	Ser	Ser	Thr 95	Ser
Gln	Ala	His 100	Tyr	Arg	Leu	Ser	Ala	Phe 105	Gly	Gln	Gln	Phe 110	Leu	Asn
Leu	Thr 115	Ala	Asn	Ala	Gly	Phe	Ile 120	Ala	Pro	Leu	Phe	Thr 125	Val	Leu
Leu	Gly 130	Thr	Pro	Gly	Val	Asn 135	Gln	Thr	Lys	Phe	Tyr 140	Ser	Glu	Glu
Ala 145	Glu	Leu	Lys	His 150	Cys	Phe	Tyr	Lys	Gly	Tyr	Val	Asn	Thr	Ser
Glu	His	Thr	Ala 165	Val	Ile	Ser	Leu	Cys 170	Ser	Gly	Met	Leu	Gly	Phe
Arg	Ser	His 180	Asp	Gly	Asp	Tyr	Phe	Ile 185	Glu	Pro	Leu	Gln 190	Ser	Asp
Glu	Gln 195	Glu	Asp	Glu	Glu	Glu	Gln 200	Asn	Lys	Pro	His	Ile 205	Ile	Arg
Arg	Ser 210	Ala	Pro	Gln	Arg	Glu	Pro 215	Ser	Thr	Gly	Arg	His 220	Ala	Asp
Thr 225	Ser	Glu	His 230	Lys	Asn	Arg	His	Ser	Lys	Asp 235	Lys	Lys	Lys	Arg
Ala	Arg	Lys	Trp 245	Gly	Glu	Arg	Ile	Asn	Leu 250	Ala	Gly	Asp	Val	Ala
Leu	Asn	Ser	Gly 255	Leu	Ala	Thr	Glu	Ala	Phe	Ser	Ala	Tyr	Gly	Lys

Val Ile Asp Gly Thr Pro Cys Gly Gln Asp Thr Asn Asp Ile Cys Val
 705 710 715 720
 Gln Gly Leu Cys Arg Gln Ala Gly Cys Asp His Val Leu Asn Ser Lys
 725 730 735
 Ala Arg Arg Asp Lys Cys Gly Val Cys Gly Gly Asp Asn Ser Ser Cys
 740 745 750
 Lys Thr Val Ala Gly Thr Phe Asn Thr Val His Tyr Gly Tyr Asn Thr
 755 760 765
 Val Val Arg Ile Pro Ala Gly Ala Thr Asn Ile Asp Val Arg Gln His
 770 775 780
 Ser Phe Ser Gly Glu Thr Asp Asp Asp Asn Tyr Leu Ala Leu Ser Ser
 785 790 795 800
 Ser Lys Gly Glu Phe Leu Leu Asn Gly Asn Phe Val Val Thr Met Ala
 805 810 815
 Lys Arg Glu Ile Arg Ile Gly Asn Ala Val Val Glu Tyr Ser Gly Ser
 820 825 830
 Glu Thr Ala Val Glu Arg Ile Asn Ser Thr Asp Arg Ile Glu Gln Glu
 835 840 845
 Leu Leu Leu Gln Val Leu Ser Val Gly Lys Leu Tyr Asn Pro Asp Val
 850 855 860
 Arg Tyr Ser Phe Asn Ile Pro Ile Glu Asp Lys Pro Gln Gln Phe Tyr
 865 870 875 880
 Trp Asn Ser His Gly Pro Trp Gln Ala Cys Ser Lys Pro Cys Gln Gly
 885 890 895
 Glu Arg Lys Arg Lys Leu Val Cys Thr Arg Glu Ser Asp Gln Leu Thr
 900 905 910
 Val Ser Asp Gln Arg Cys Asp Arg Leu Pro Gln Pro Gly His Ile Thr
 915 920 925
 Glu Pro Cys Gly Thr Asp Cys Asp Leu Arg Trp His Val Ala Ser Arg
 930 935 940
 Ser Glu Cys Ser Ala Gln Cys Gly Leu Gly Tyr Arg Thr Leu Asp Ile
 945 950 955 960
 Tyr Cys Ala Lys Tyr Ser Arg Leu Asp Gly Lys Thr Glu Lys Val Asp
 965 970 975
 Asp Gly Phe Cys Ser Ser His Pro Lys Pro Ser Asn Arg Glu Lys Cys
 980 985 990
 Ser Gly Glu Cys Asn Thr Gly Gly Trp Arg Tyr Ser Ala Trp Thr Glu
 995 1000 1005
 Cys Lys Ser Lys Ser Cys Asp Gly Gly Thr Gln Arg Arg Arg Ala Ile
 1010 1015 1020
 Cys Val Asn Thr Arg Asn Asp Val Leu Asp Asp Ser Lys Cys Thr His
 1025 1030 1035 1040
 Gln Glu Lys Val Thr Ile Gln Arg Cys Ser Glu Phe Pro Cys Pro Gln
 1045 1050 1055
 Trp Lys Ser Gly Asp Trp Ser Glu Val Arg Trp Glu Gly Cys Tyr Phe
 1060 1065 1070
 Pro

<210> 28

<211> 951

<212> PRT

<213> Mus musculus

<400> 28

Met Gly Asp Val Gln Arg Ala Ala Arg Ser Arg Gly Ser Leu Ser Ala

1	5	10	15
His Met Leu Leu Leu Leu Leu Ala Ser Ile Thr Met Leu Leu Cys Ala			
20	25	30	
Arg Gly Ala His Gly Arg Pro Thr Glu Glu Asp Glu Glu Leu Val Leu			
35	40	45	
Pro Ser Leu Glu Arg Ala Pro Gly His Asp Ser Thr Thr Thr Arg Leu			
50	55	60	
Arg Leu Asp Ala Phe Gly Gln Gln Leu His Leu Lys Leu Gln Pro Asp			
65	70	75	80
Ser Gly Phe Leu Ala Pro Gly Phe Thr Leu Gln Thr Val Gly Arg Ser			
85	90	95	
Pro Gly Ser Glu Ala Gln His Leu Asp Pro Thr Gly Asp Leu Ala His			
100	105	110	
Cys Phe Tyr Ser Gly Thr Val Asn Gly Asp Pro Gly Ser Ala Ala Ala			
115	120	125	
Leu Ser Leu Cys Glu Gly Val Arg Gly Ala Phe Tyr Leu Gln Gly Glu			
130	135	140	
Glu Phe Phe Ile Gln Pro Ala Pro Gly Val Ala Thr Glu Arg Leu Ala			
145	150	155	160
Pro Ala Val Pro Glu Glu Glu Ser Ser Ala Arg Pro Gln Phe His Ile			
165	170	175	
Leu Arg Arg Arg Arg Arg Gly Ser Gly Gly Ala Lys Cys Gly Val Met			
180	185	190	
Asp Asp Glu Thr Leu Pro Thr Ser Asp Ser Arg Pro Glu Ser Gln Asn			
195	200	205	
Thr Arg Asn Gln Trp Pro Val Arg Asp Pro Thr Pro Gln Asp Ala Gly			
210	215	220	
Lys Pro Ser Gly Pro Gly Ser Ile Arg Lys Lys Arg Phe Val Ser Ser			
225	230	235	240
Pro Arg Tyr Val Glu Thr Met Leu Val Ala Asp Gln Ser Met Ala Asp			
245	250	255	
Phe His Gly Ser Gly Leu Lys His Tyr Leu Leu Thr Leu Phe Ser Val			
260	265	270	
Ala Ala Arg Phe Tyr Lys His Pro Ser Ile Arg Asn Ser Ile Ser Leu			
275	280	285	
Val Val Val Lys Ile Leu Val Ile Tyr Glu Glu Gln Lys Gly Pro Glu			
290	295	300	
Val Thr Ser Asn Ala Ala Leu Thr Leu Arg Asn Phe Cys Asn Trp Gln			
305	310	315	320
Lys Gln His Asn Ser Pro Ser Asp Arg Asp Pro Glu His Tyr Asp Thr			
325	330	335	
Ala Ile Leu Phe Thr Arg Gln Asp Leu Cys Gly Ser His Thr Cys Asp			
340	345	350	
Thr Leu Gly Met Ala Asp Val Gly Thr Val Cys Asp Pro Ser Arg Ser			
355	360	365	
Cys Ser Val Ile Glu Asp Asp Gly Leu Gln Ala Ala Phe Thr Thr Ala			
370	375	380	
His Glu Leu Gly His Val Phe Asn Met Pro His Asp Asp Ala Lys His			
385	390	395	400
Cys Ala Ser Leu Asn Gly Val Thr Gly Asp Ser His Leu Met Ala Ser			
405	410	415	
Met Leu Ser Ser Leu Asp His Ser Gln Pro Trp Ser Pro Cys Ser Ala			
420	425	430	
Tyr Met Val Thr Ser Phe Leu Asp Asn Gly His Gly Glu Cys Leu Met			
435	440	445	

Asp	Lys	Pro	Gln	Asn	Pro	Ile	Lys	Leu	Pro	Ser	Asp	Leu	Pro	Gly	Thr
450						455					460				
Leu	Tyr	Asp	Ala	Asn	Arg	Gln	Cys	Gln	Phe	Thr	Phe	Gly	Glu	Glu	Ser
465				470						475					480
Lys	His	Cys	Pro	Asp	Ala	Ala	Ser	Thr	Cys	Thr	Thr	Leu	Trp	Cys	Thr
			485						490					495	
Gly	Thr	Ser	Gly	Gly	Leu	Leu	Val	Cys	Gln	Thr	Lys	His	Phe	Pro	Trp
			500					505					510		
Ala	Asp	Gly	Thr	Ser	Cys	Gly	Glu	Gly	Lys	Trp	Cys	Val	Ser	Gly	Lys
		515				520						525			
Cys	Val	Asn	Lys	Thr	Asp	Met	Lys	His	Phe	Ala	Thr	Pro	Val	His	Gly
	530					535					540				
Ser	Trp	Gly	Pro	Trp	Gly	Pro	Trp	Gly	Asp	Cys	Ser	Arg	Thr	Cys	Gly
545				550						555					560
Gly	Gly	Val	Gln	Tyr	Thr	Met	Arg	Glu	Cys	Asp	Asn	Pro	Val	Pro	Lys
			565						570					575	
Asn	Gly	Gly	Lys	Tyr	Cys	Glu	Gly	Lys	Arg	Val	Arg	Tyr	Arg	Ser	Cys
			580					585					590		
Asn	Ile	Glu	Asp	Cys	Pro	Asp	Asn	Asn	Gly	Lys	Thr	Phe	Arg	Glu	Glu
		595				600						605			
Gln	Cys	Glu	Ala	His	Asn	Glu	Phe	Ser	Lys	Ala	Ser	Phe	Gly	Asn	Glu
	610					615					620				
Pro	Thr	Val	Glu	Trp	Thr	Pro	Lys	Tyr	Ala	Gly	Val	Ser	Pro	Lys	Asp
625				630						635					640
Arg	Cys	Lys	Leu	Thr	Cys	Glu	Ala	Lys	Gly	Ile	Gly	Tyr	Phe	Phe	Val
			645						650					655	
Leu	Gln	Pro	Lys	Val	Val	Asp	Gly	Thr	Pro	Cys	Ser	Pro	Asp	Ser	Thr
		660						665					670		
Ser	Val	Cys	Val	Gln	Gly	Gln	Cys	Val	Lys	Ala	Gly	Cys	Asp	Arg	Ile
		675				680						685			
Ile	Asp	Ser	Lys	Lys	Lys	Phe	Asp	Lys	Cys	Gly	Val	Cys	Gly	Gly	Asn
	690					695					700				
Gly	Ser	Thr	Cys	Lys	Lys	Met	Ser	Gly	Ile	Val	Thr	Ser	Thr	Arg	Pro
705				710						715					720
Gly	Tyr	His	Asp	Ile	Val	Thr	Ile	Pro	Ala	Gly	Ala	Thr	Asn	Ile	Glu
			725						730					735	
Val	Lys	His	Arg	Asn	Gln	Arg	Gly	Ser	Arg	Asn	Asn	Gly	Ser	Phe	Leu
		740						745					750		
Ala	Ile	Arg	Ala	Ala	Asp	Gly	Thr	Tyr	Ile	Leu	Asn	Gly	Asn	Phe	Thr
		755				760						765			
Leu	Ser	Thr	Leu	Glu	Gln	Asp	Leu	Thr	Tyr	Lys	Gly	Thr	Val	Leu	Arg
	770					775					780				
Tyr	Ser	Gly	Ser	Ser	Ala	Ala	Leu	Glu	Arg	Ile	Arg	Ser	Phe	Ser	Pro
785				790						795					800
Leu	Lys	Glu	Pro	Leu	Thr	Ile	Gln	Val	Leu	Met	Val	Gly	His	Ala	Leu
			805						810					815	
Arg	Pro	Lys	Ile	Lys	Phe	Thr	Tyr	Phe	Met	Lys	Lys	Lys	Thr	Glu	Ser
		820						825					830		
Phe	Asn	Ala	Ile	Pro	Thr	Phe	Ser	Glu	Trp	Val	Ile	Glu	Glu	Trp	Gly
	835					840						845			
Glu	Cys	Ser	Lys	Thr	Cys	Gly	Ser	Gly	Trp	Gln	Arg	Arg	Val	Val	Gln
	850					855					860				
Cys	Arg	Asp	Ile	Asn	Gly	His	Pro	Ala	Ser	Glu	Cys	Ala	Lys	Glu	Val
865				870						875					880
Lys	Pro	Ala	Ser	Thr	Arg	Pro	Cys	Ala	Asp	Leu	Pro	Cys	Pro	His	Trp

<210> 32
<211> 6
<212> PRT
<213> Unknown

<220>
<223> Semiconserved sequence of ADAMTS protein domain
that binds to the extracellular matrix

<400> 32
Phe Arg Glu Glu Gln Cys
1 5

<210> 33
<211> 18
<212> DNA
<213> Artificial Sequence

<220>
<223> Oligonucleotide derived from analysis of the
sequences from ADAMTS-1 (mouse) and ADAMTS-3 (rat)

<221> misc_feature
<222> (1)...(18)
<223> n = A,T,C or G

<400> 33
ttymgngarg arcartgy

18

<210> 34
<211> 18
<212> DNA
<213> Artificial Sequence

<220>
<223> Oligonucleotide derived from analysis of the
sequences from ADAMTS-1 (mouse) and ADAMTS-3 (rat)

<221> misc_feature
<222> (1)...(18)
<223> n = A,T,C or G

<400> 34
rcanayncrr cayttrtc

18

<210> 35
<211> 4
<212> PRT
<213> Homos sapien

<220>
<223> Consensus catalytic sequence site based on ADAM
and snake venom metalloproteases

<221> VARIANT
<222> (3) ... (3)
<223> Xaa = Lysine or Arginine

<221> VARIANT
<222> (1) ... (4)
<223> Xaa = Any Amino Acid

<400> 35
Arg Xaa Xaa Arg
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<210> 36
<211> 7
<212> PRT
<213> Unknown

<220>
<223> Conserved heparin binding segment of internal TSP1
motif of ADAM-TS family members

<221> VARIANT
<222> (2) ... (2)
<223> Xaa = Serine or Glycine

<221> VARIANT
<222> (1) ... (7)
<223> Xaa = Any Amino Acid

<400> 36
Trp Xaa Xaa Trp Ser Xaa Trp
1 5

<210> 37
<211> 6
<212> PRT
<213> Unknown

<220>
<223> Conserved heparin binding segment of internal TSP1
motif of ADAM-TS family members

<400> 37
Cys Ser Val Thr Cys Gly
1 5

<210> 38
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Primer

<400> 38

caggggaaac agacgatgac aact

24

<210> 39

<211> 21

<212> DNA

<213> Artificial Sequence

<220>

<223> Primer

<400> 39

tgcggttaacc caagccacac t

21

<210> 40

<211> 21

<212> DNA

<213> Artificial Sequence

<220>

<223> Primer

<400> 40

gtgcgctggg tccctaaata c

21

<210> 41

<211> 21

<212> DNA

<213> Artificial Sequence

<220>

<223> Primer

<400> 41

aaaatcacag gttggcagcg g

21

<210> 42

<211> 12

<212> PRT

<213> Unknown

<220>

<223> Zn binding site

<400> 42

His Glu Leu Gly His Asn Leu Gly Ile Arg His Asp

1

5

10

<210> 43

<211> 12

<212> PRT

<213> Unknown

<220>

<223> Zn binding site

<400> 43

His Glu Leu Gly His Asn Phe Gly Ala Glu His Asp
1 5 10

<210> 44

<211> 12

<212> PRT

<213> Unknown

<220>

<223> Zn binding site

<400> 44

His Glu Ile Gly His Asn Phe Gly Ser Pro His Asp
1 5 10

<210> 45

<211> 12

<212> PRT

<213> Homo sapien

<400> 45

His Glu Leu Gly His Val Phe Asn Met Pro His Asp
1 5 10

<210> 46

<211> 12

<212> PRT

<213> Homo sapien

<400> 46

His Glu Thr Gly His Val Leu Gly Met Glu His Asp
1 5 10

<210> 47

<211> 12

<212> PRT

<213> Homo sapien

<400> 47

His Glu Leu Gly His Val Phe Asn Met Leu His Asp
1 5 10

<210> 48

<211> 12

<212> PRT

<213> Homo sapien

<400> 48

His Glu Ile Gly His Leu Leu Gly Leu Ser His Asp
1 5 10

<210> 49

<211> 12

<212> PRT

<213> Homo sapien

<400> 49

His Glu Leu Gly His Val Phe Asn Met Pro His Asp
1 5 10

<210> 50

<211> 12

<212> PRT

<213> C. elegans

<400> 50

His Glu Leu Gly His Val Phe Ser Ile Pro His Asp
1 5 10

<210> 51

<211> 12

<212> PRT

<213> Unknown

<220>

<223> Consensus catalytic sequence site based on ADAM
and snake venom metalloproteases

<221> VARIANT

<222> (1)...(12)

<223> Xaa = Any Amino Acid

<400> 51

His Glu Xaa Gly His Xaa Xaa Gly Xaa Xaa His Asp
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